

JANUARY, 1958

VOL. 75, NO. 1

*American  
Journal  
of*

**OBSTETRICS  
AND GYNECOLOGY**

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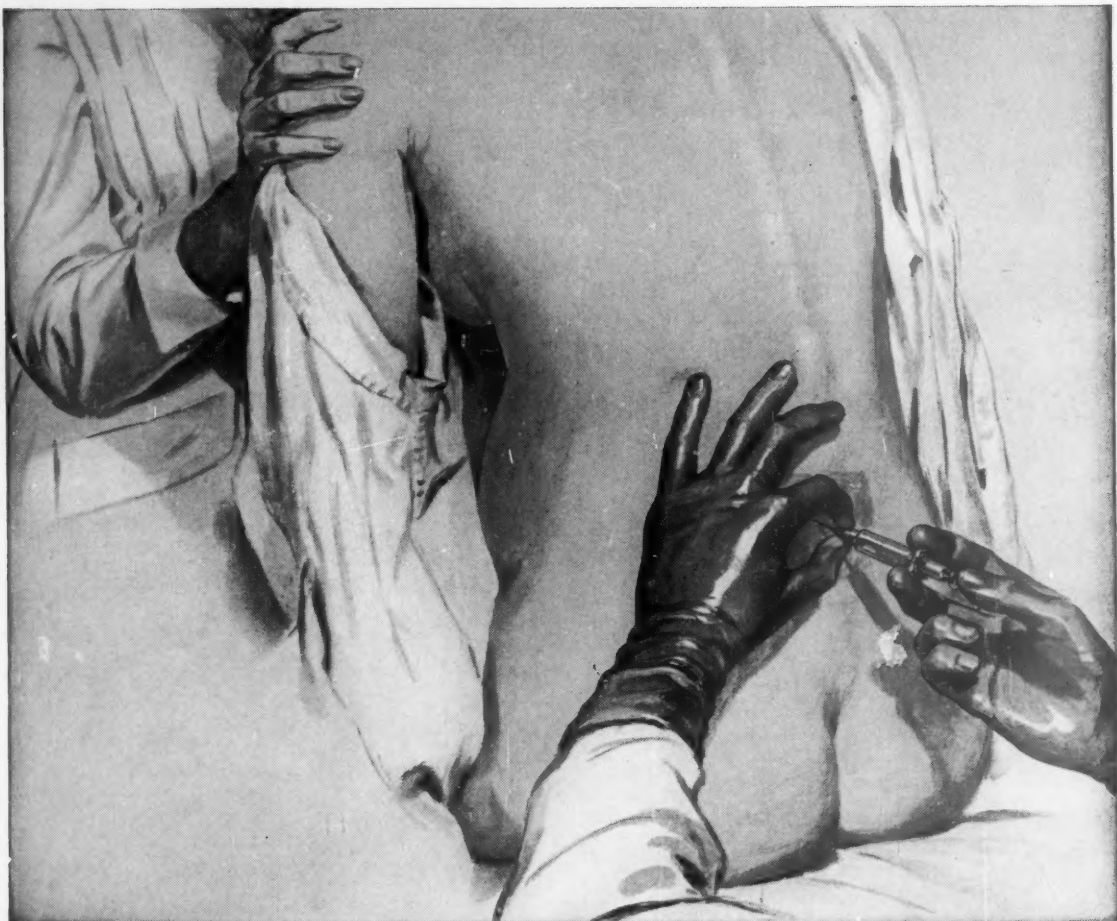
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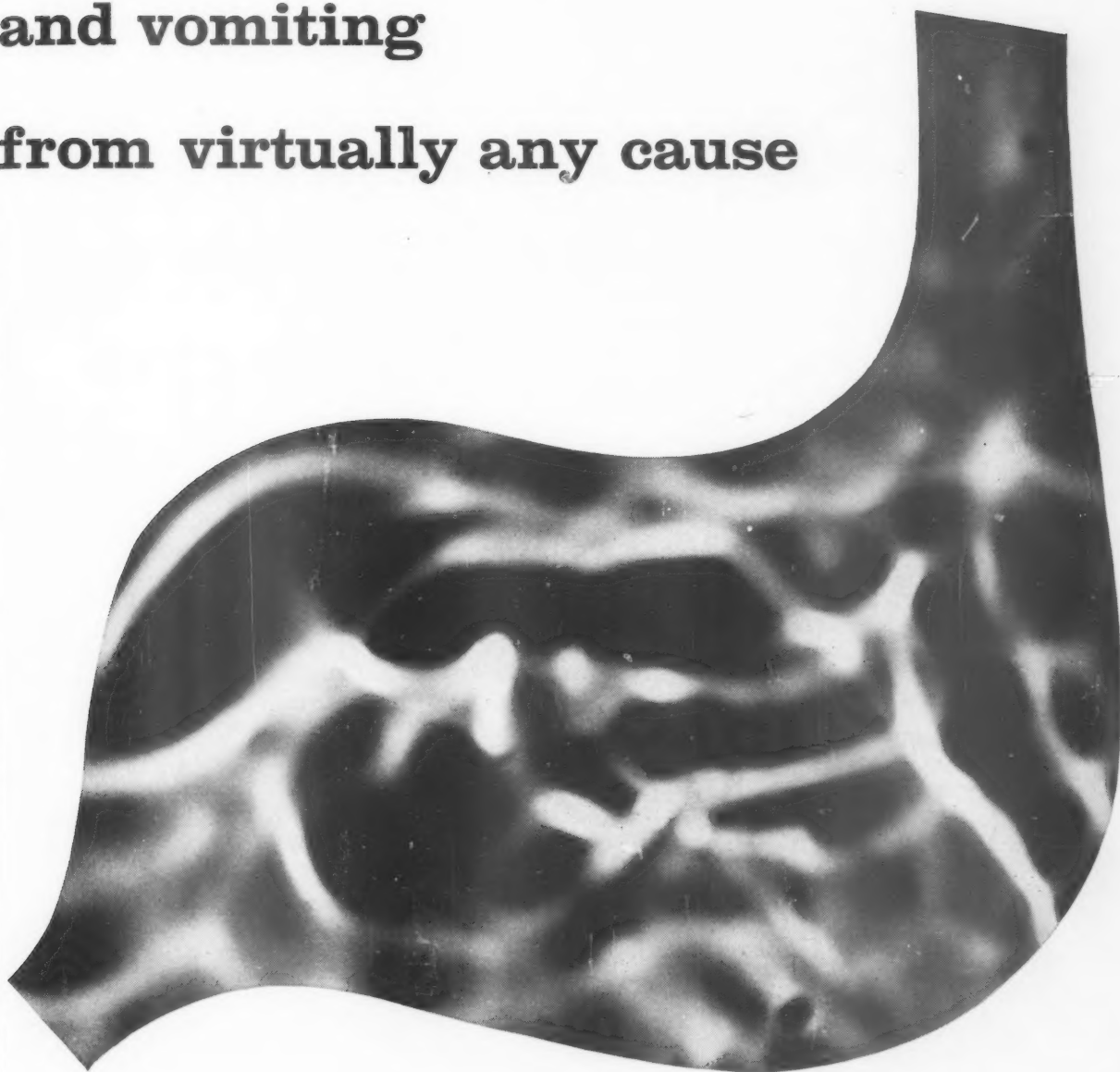
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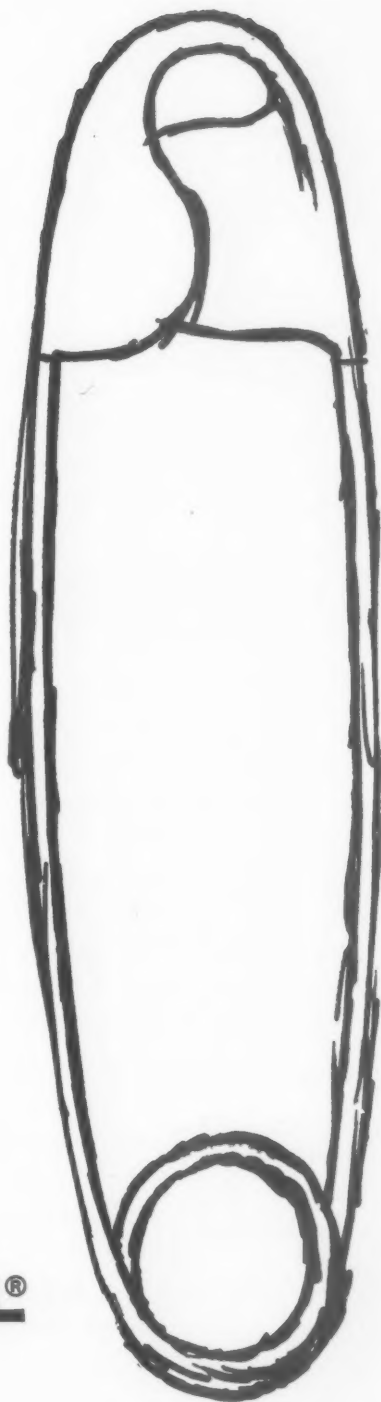
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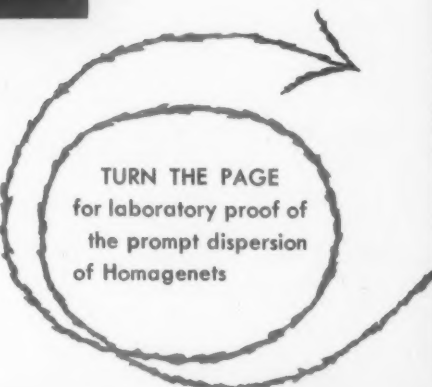
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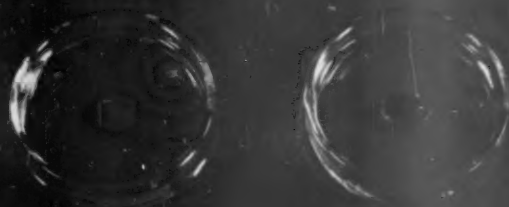
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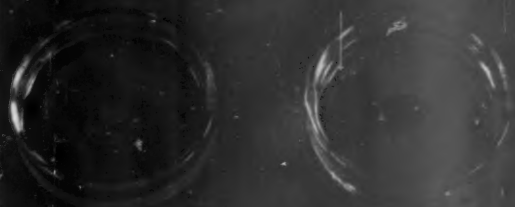
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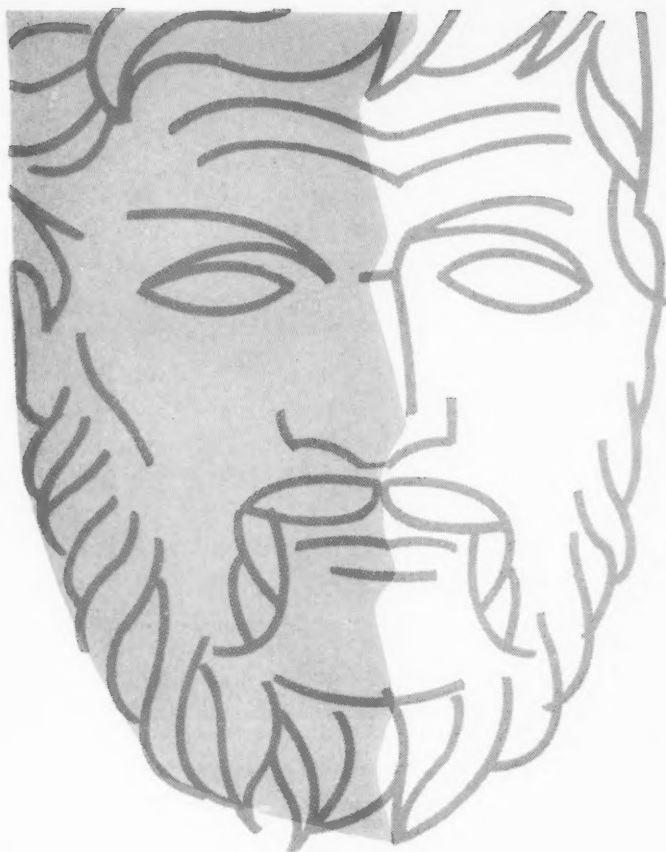


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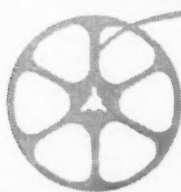
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TROCINATE, a clinically proved safe spasmolytic, especially potent, in pharmacologic studies, in relieving spasm of the uterus (J. Pharm. Exp. Ther. 89:131).

THEOPHYLLINE, a diuretic to combat fluid retention and uterine tissue edema, important etiologically in the premenstrual tension-dysmenorrhea syndrome.

PYRILAMINE MALEATE, an antihistaminic to combat any allergic factor.

IN EACH PINK AND GRAY CAPSULE TROCINATE 100 MGMS., THEOPHYLLINE 100 MGMS., PYRILAMINE MALEATE 25 MGMS.

IN BOTTLES OF 25 AND 100 CAPSULES

Directions: One capsule after each meal and at bedtime, beginning 4 days before onset of menstruation, and continuing through first day of flow.

*Wm. P. Poythress & Co., Inc.*

ETHICAL PHARMACEUTICALS • RICHMOND 17, VIRGINIA

AN IMPORTANT ADVANCE IN MENOPAUSAL THERAPY

**Because** it replaces *half* control with *full* control.  
**Because** it treats the *whole* menopausal syndrome.  
**Because** one prescription manages *both* the  
psychic and somatic symptoms.

*Two-dimensional  
treatment  
of  
the*



SUPPLIED: Bottles of 60 tablets.  
Each tablet contains:

MILTOWN® (meprobamate, Wallace) ..... 400 mg.  
2-methyl-2-n-propyl-1,3-propanediol dicarbamate.  
U. S. Patent No. 2,724,720.  
Conjugated Estrogens (equine) ..... 0.4 mg.  
Licensed under U. S. Patent No. 2,429,398.

DOSAGE: One tablet t.i.d. in 21-day courses with one week rest periods.  
Should be adjusted to individual requirements.  
Samples and literature on request.

**“Milprem”**

MILTOWN® + CONJUGATED ESTROGENS (EQUINE)  
A Proven Tranquillizer    A Proven Estrogen

W<sup>®</sup> WALLACE LABORATORIES, New Brunswick, N. J.  
who discovered and introduced Miltown, the original meprobamate.





# Psychic cycle

Anxiety, tension, and related symptoms exist in most gynecologic disturbances.

Symptoms of premenstrual tension (irritability, nervousness, headaches) were completely relieved with 'Miltown' in 78% of patients, and substantially relieved in all others studied.<sup>1</sup>

Patients with tension symptoms during menstruation became symptom-free on 'Miltown' therapy.<sup>2</sup>

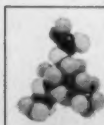
'Miltown' *relaxes both mind and skeletal muscle* and alleviates somatic symptoms of anxiety, tension, and fear (usual dosage: 400 mg. q.i.d.). 'Miltown' therapy is notably safe, even in pregnancy,<sup>3</sup> and does not impair mental or physical efficiency.

#### References:

1. Pennington, V. M.: Meprobamate (Miltown) in premenstrual tension. *J.A.M.A.* 164:638, June 8, 1957.
2. Selling, L. S.: Clinical study of a new tranquilizing drug: use of Miltown (2-methyl-2-n-propyl-1,3-propanediol dicarbamate). *J.A.M.A.* 157:1594, April 30, 1955.
3. Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. *Obst. & Gynec.* 9:703, June 1957.

# Miltown®

CM-5793



THE ORIGINAL MEPROBAMATE  
DISCOVERED & INTRODUCED BY  
WALLACE LABORATORIES  
NEW BRUNSWICK, NEW JERSEY



# Preception

simple, effective conception control



CEPTIN  
nal gel



*For the first time ...*

**YOU  
CAN TURN OFF  
THE COUGH  
UNTIL  
MORNING**

# TUSSIONEX<sup>TM</sup>

A 'Strasionic' Release Product • Dihydrocodeinone Resin—Phenyltoloxamine Resin

## 8-12 HOUR CONTROL WITH A SINGLE DOSE

through sustained 'Strasionic' release.

Suppresses nighttime sleep-robbing, daytime distracting, useless coughs without interfering with the protective cough mechanism.

Over 12,000 clinical observations<sup>1,2,3,4</sup> demonstrate its wide field of usefulness in ages ranging from 3 months to more than 70 years.

### REFERENCES

(1) Chan, Y. T. and Hays, E. E., The American Journal of the Medical Sciences, August 1957; (2) Townsend, E. H., Jr., In Press; (3) Weismiller, F., In Press; (4) Cass, Leo J. and Frederik, W. S., In Press.

Now Available  
on Your Prescription



#### EACH TUSSIONEX TABLET CONTAINS

5 mg. Dihydrocodeinone as  
a resin complex

10 mg. Phenyltoloxamine as  
a resin complex

Stock bottle of 100



#### EACH TEASPOON (5cc) TUSSIONEX LIQUID CONTAINS

5 mg. Dihydrocodeinone as  
a resin complex

10 mg. Phenyltoloxamine as  
a resin complex

Stock bottle of 16 oz.

#### SUGGESTED DOSE

One tablet or teaspoon (5cc) q12h

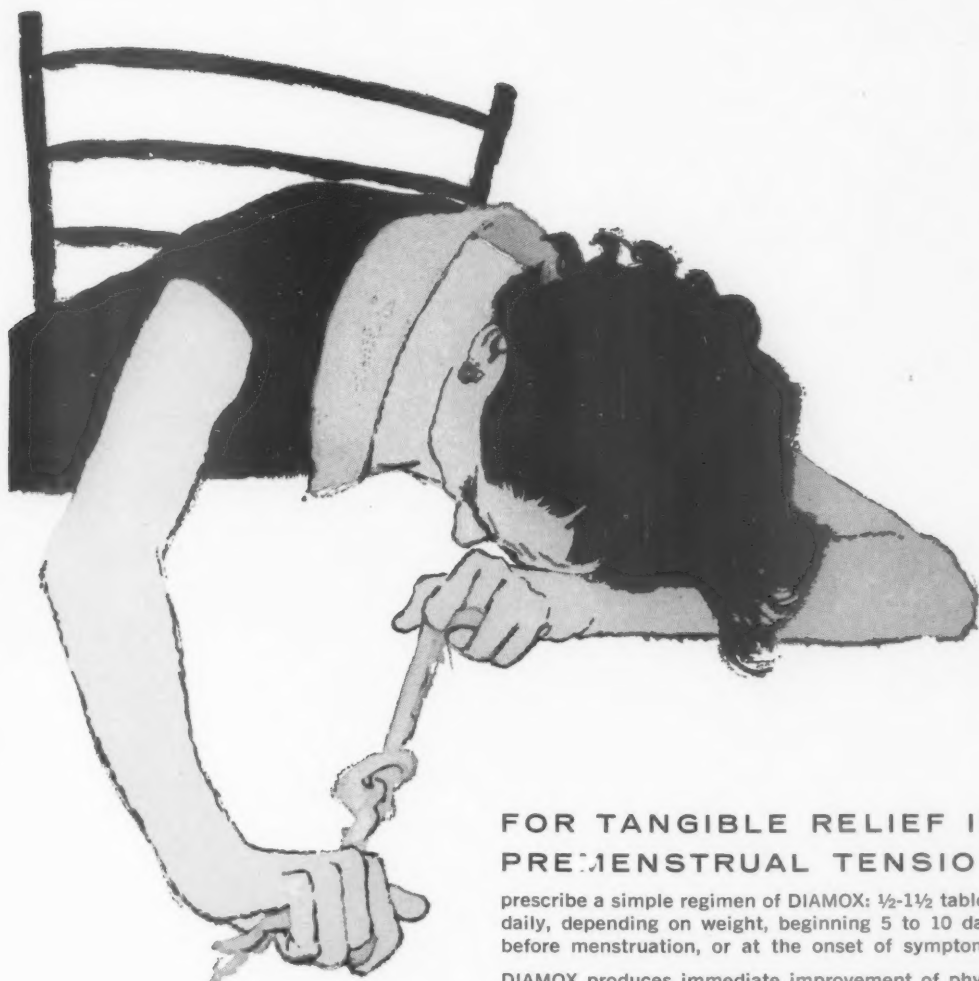
Rx only. Class B taxable narcotic.

## STRASENBURGH

Originators of 'Strasionic' (sustained ionic) Release

R. J. STRASENBURGH CO., ROCHESTER, N. Y., U.S.A.





## FOR TANGIBLE RELIEF IN PREMENSTRUAL TENSION

prescribe a simple regimen of DIAMOX:  $\frac{1}{2}$ -1 $\frac{1}{2}$  tablets daily, depending on weight, beginning 5 to 10 days before menstruation, or at the onset of symptoms.

DIAMOX produces immediate improvement of physical and emotional well-being in these patients by prompt control of the edema frequently associated with premenstrual tension.

A versatile, well-tolerated diuretic, DIAMOX is highly effective in the mobilization of edema fluid, and in the prevention of fluid accumulation. A single dose is active for 6 to 12 hours, offering convenient day-time diuresis. Excretion by the kidney is usually complete within 12 hours with no cumulative effects.

**SUPPLIED:** Scored Tablets of 250 mg. (Also in ampuls of 500 mg. for parenteral use).

**DIAMOX SYRUP:** 250 mg. per 5 cc. teaspoonful, peach flavor. Bottles of 4 fluid ounces.

nonmercurial diuretic

# Diamox\*

ACETAZOLAMIDE LEDERLE



LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY  
PEARL RIVER, NEW YORK

\*Reg. U. S. Pat. Off.



for the  
early  
"stand-by"  
bottle...



...one thing bothers me about  
leaving the hospital. My milk  
is just starting. Suppose, in  
the excitement of going home, I  
don't have enough milk and  
the baby goes hungry?...

# SIMILAC®

as the  
compatible  
supplement



This advertisement conforms  
to the Code for Advertising  
of the Physicians' Council for  
Information on Child Health.



ROSS LABORATORIES,  
Columbus 16, Ohio

## *Feeling at home*

During the first days at home with her new baby, the mother may find her milk supply is low, from excitement and nervousness in the face of readjustments she must make at home. You can reassure her that Similac is closely equivalent to her own milk, and that breast feedings can be compatibly replaced with Similac feedings.

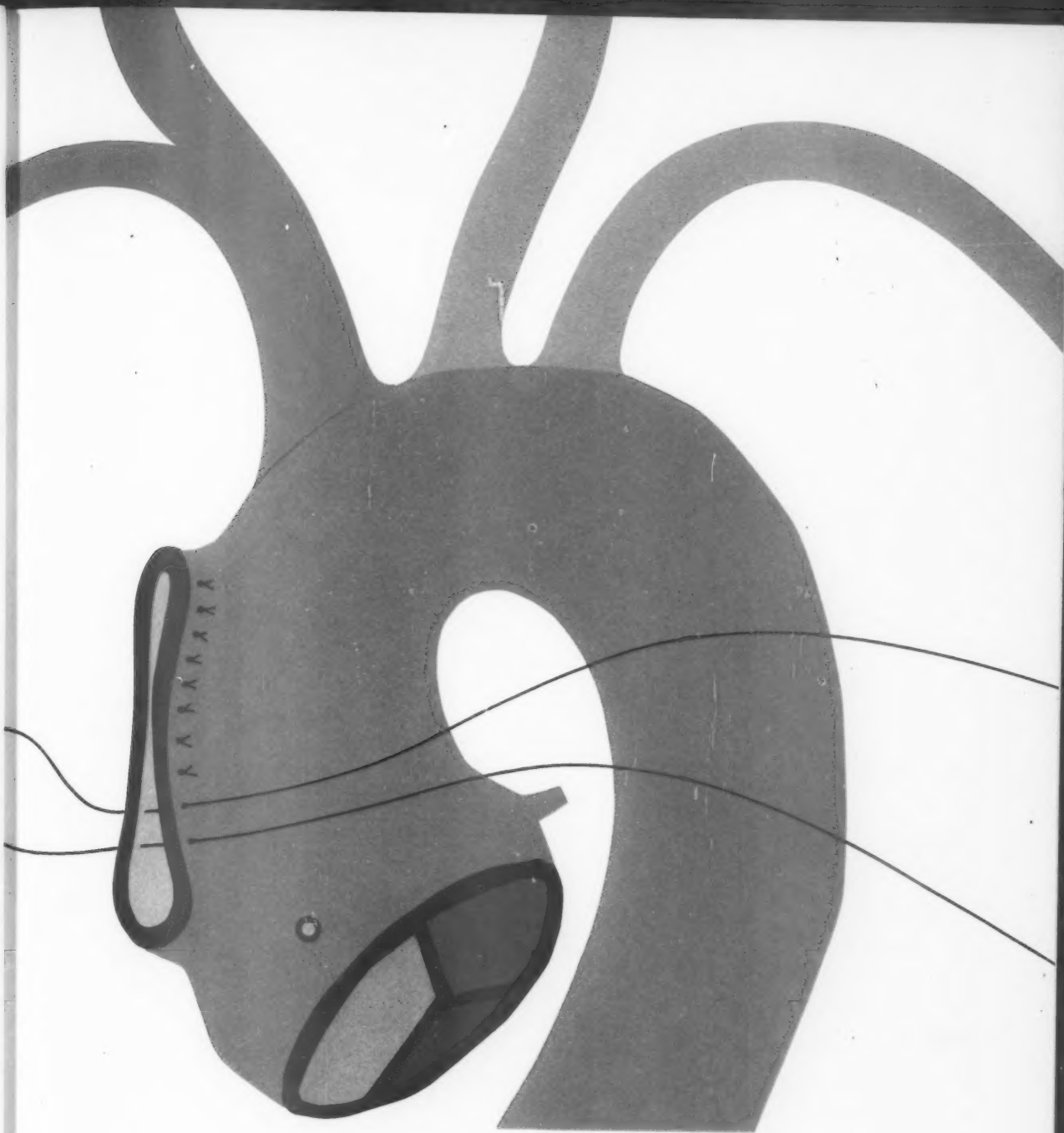
## *A compatible supplement*

Similac provides a suitable and logical supplement to breast milk. Physiologic levels of essential fatty acids, protein and carbohydrate in the same balanced proportion as in breast milk, plus all known essential vitamins are provided in the formula.

With the reassurance that her infant will not want for good nutrition, the breast-feeding mother may feel more confident and at ease in the early feeding situation. The tensions of readjustment may be more easily and confidently met with reliance on Similac for the "stand-by" bottle. This reassurance even may help her nurse the baby longer.

*Compatible infant feeding . . .  
breast feeding and Similac*

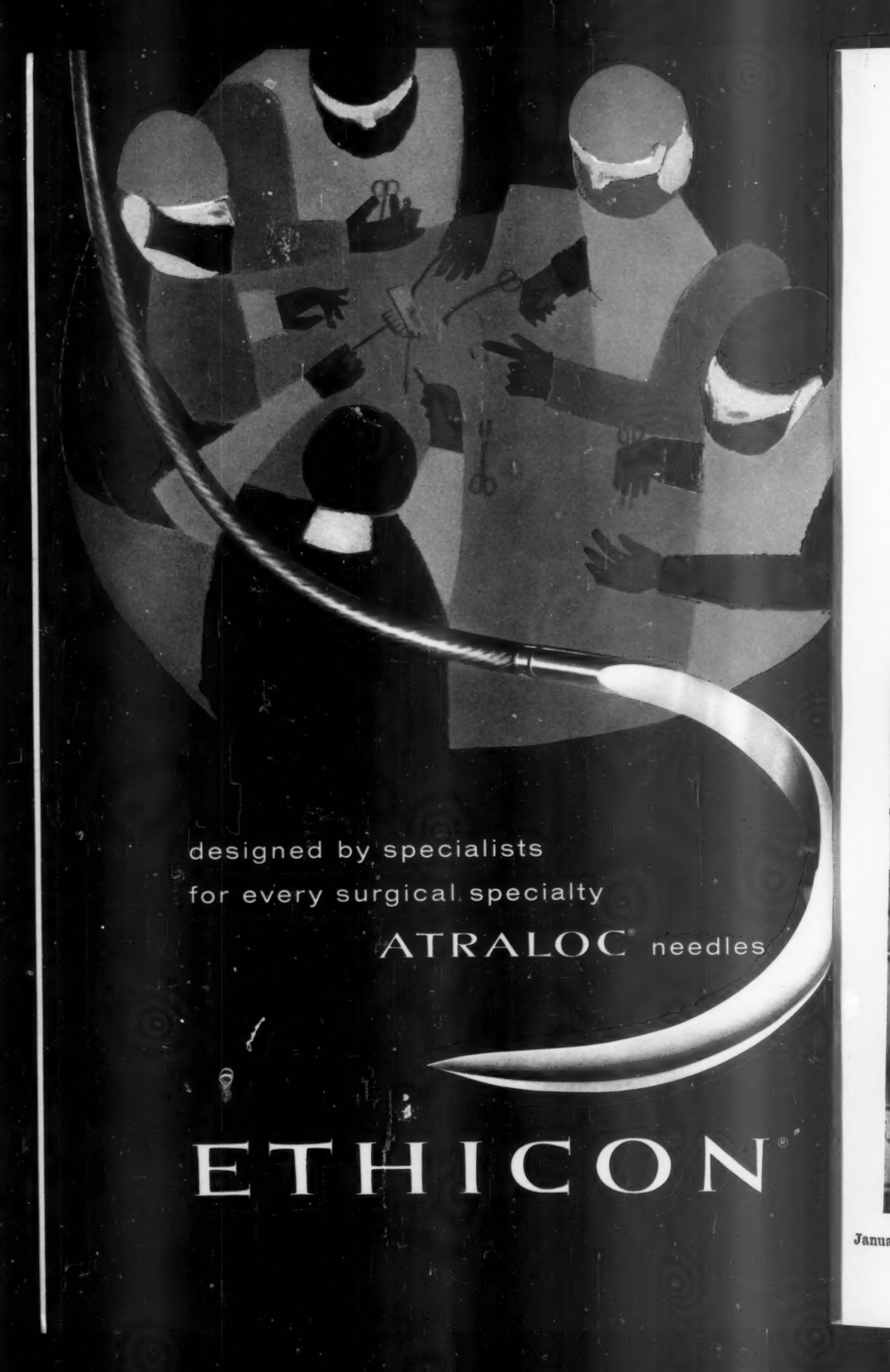




setting new standards

**ETHICON®**

sutures



designed by specialists  
for every surgical specialty

ATRALOC® needles

ETHICON®

# In Dysmenorrhea

R<sub>x</sub> the analgesic which contains Benzedrine® Sulfate (amphetamine sulfate, S.K.F.), "the most satisfactory antispasmodic"<sup>1</sup>

## EDRISAL<sup>®</sup>

Antispasmodic—Antidepressant—Analgesic

**2 tablets every 3 hours**

Also available: 'Edrisal with Codeine' (¼ gr. & ½ gr.)



1. Janney: Medical Gynecology, ed. 2.





**safety and efficiency  
proved in more than**

**2,000,000**

## **TRANSFUSIONS**

**THE RECORD OF THE R48 PRESSURE PUMP SET SPEAKS FOR ITSELF.** First set to make pressure transfusion safe for the patient, the disposable Plexitron R48 is being specified in more hospitals every day . . . throughout the world.

*Emergency pressure is instantly available . . . simply squeeze the drip chamber. The degree of pressure and speed of transfusion varies with the degree of pumping action. The ball-float safety valve operates only with fluids . . . you can't pump air. Set can be returned to gravity drip easily, at any time.*

*Only filtered blood reaches the patient. Fine-mesh filter, of exclusive construction and design, provides maximum filtration area and assures efficient removal of particulate matter in both routine and emergency transfusions.*

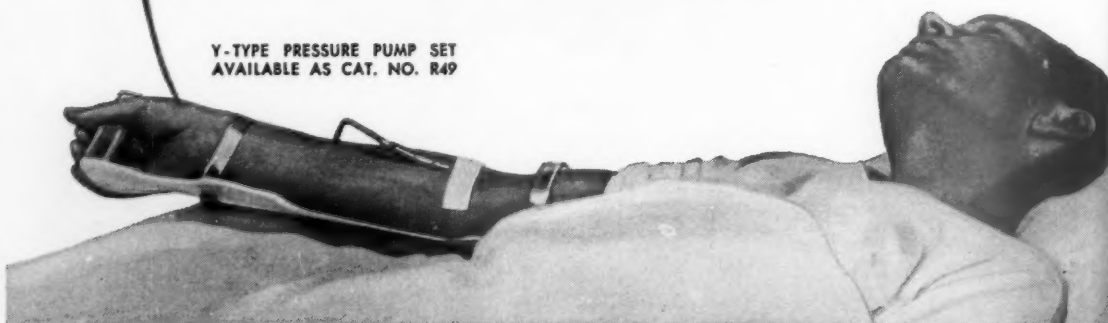
*Literature, samples and demonstration on request*

**BAXTER LABORATORIES, INC.**

**MORTON GROVE, ILL.**

**DISTRIBUTED AND AVAILABLE ONLY IN THE 37 STATES EAST OF THE ROCKIES (except in the city of El Paso, Texas) THROUGH AMERICAN HOSPITAL SUPPLY CORPORATION**  
SCIENTIFIC PRODUCTS DIVISION GENERAL OFFICES • EVANSTON, ILLINOIS

**Y-TYPE PRESSURE PUMP SET  
AVAILABLE AS CAT. NO. R49**



**superior vulvovaginal therapy**  
with

# **trichotine®**

**a surface-active detergent**  
which dissolves the viscid film

**a bactericide and fungicide**  
which penetrates and destroys  
the microorganisms

**an antipruritic**  
for prompt relief from itching  
and discomfort

**a psychic and aesthetic adjunct**  
providing an immediate sense  
of well-being

## **Indications:**

**Vaginitis and Vulvovaginitis** — nonspecific,  
trichomonal, monilial, senile, diabetic, postoperative

**Cervicitis** — subacute and chronic

**Pruritus Vulvae** — hot pack applications

**Office Clean-up** — concentrated solutions

**Hygienic Irrigations** — postcoital, postmenstrual

## **suggestion:**

Upon retiring, a TRICHOTINE douche followed by a  
VACID suppository provides maximum effectiveness and  
24-hour pH control.

The TRICHOTINE formula contains sodium lauryl  
sulfate, sodium perborate, sodium borate, thymol, menthol,  
eucalyptol and methyl salicylate.

*samples and literature upon request.*

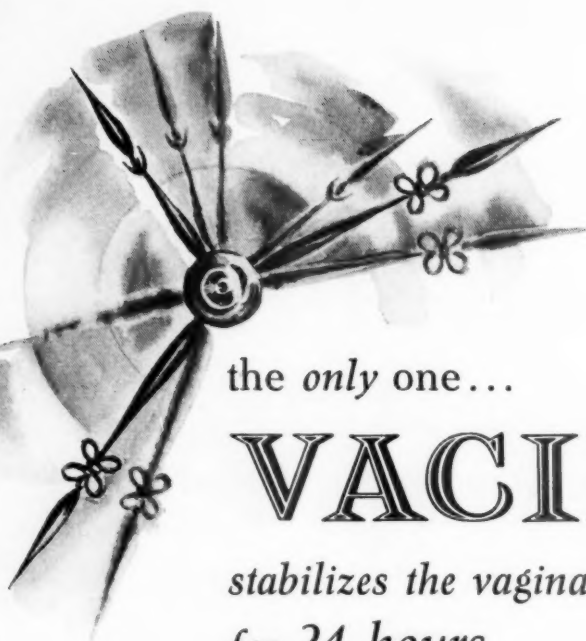
**The Fesler Co., Inc.**

375 Fairfield Ave.

Stamford, Conn.



**R<sub>x</sub> VACID**  
(FESLER)



the *only* one...

**VACID<sup>®</sup>**

*stabilizes the vaginal pH  
for 24 hours*

Extensive clinical experience demonstrates the therapeutic value of the continual maintenance of the normal physiologic pH in the treatment of trichomonal, monilial, and non-specific bacterial infections and in cervicitis.

*Only* Vacid provides a high capacity cationic exchange resin accurately buffered to stabilize the vaginal pH range at 4.0-4.5 for twenty-four hours.

**Indications:** **IN VAGINITIS** — trichomonal, monilial, non-specific  
**CERVICITIS** — subacute and chronic, including eversion  
**POSTCAUTERY** and **POSTCONIZATION**  
**PREGNANCY** and **POSTPARTUM** — prophylactically and in infections.

**Suggestion:** Upon retiring, a Vacid suppository preceded by a Trichotone douche provides maximum effectiveness and 24-hour pH control.

**FORMULA** — Each Vacid suppository contains a high capacity polyacrylic cationic exchange resin (activated and buffered) combined with lactose.

*samples and literature upon request*

**The Fesler Co., Inc.**

375 Fairfield Ave.

Stamford, Conn.

*she needs support, too...*  
*during pregnancy and throughout lactation*



# NATABEC® KAPSEALS®

vitamin-mineral combination

She balances her nutritional needs by adding to her diet NATABEC Kapseals prescribed by her physician. As a dietary supplement, NATABEC provides vitamins and minerals for nutritional support, helping to promote better present and future health for the mother and her child.

each NATABEC Kapsel contains:

Calcium carbonate	600 mg.	Synkamin® (vitamin K)	
Ferrous sulfate	150 mg.	(as the hydrochloride)	0.5 mg.
Vitamin D	400 units	Butin	10 mg.
Vitamin B <sub>1</sub> (thiamine) mesconitate	3 c.c.	Nicotinamide (niacinamide)	10 mg.
Vitamin B <sub>2</sub> (riboflavin)	2 mg.	Vitamin B <sub>6</sub> (pyridoxine hydrochloride)	2 mg.
Vitamin B <sub>12</sub> (crystalline)	2 mcg.	Vitamin C (ascorbic acid)	50 mg.
Folic acid	1 mg.	Vitamin A	5,000 units
		Intrinsic factor concentrate	5 mg.

#### **dosage**

As a dietary supplement during pregnancy and throughout lactation, one or more Kapseals daily. Available in bottles of 100 and 1,000.



**PARKE, DAVIS & COMPANY**  
 DETROIT 32, MICHIGAN

© 1974

# Easier Childbirth

The  
National  
Drug  
Company  
is proud to announce  
a significant  
advance  
in the relief  
of pain  
and the  
shortening of labor  
in childbirth.



## Cervilaxin

NATIONAL brand of relaxin

*for shorter labor,  
...easier delivery*

## Answers to some questions on Cervilaxin<sup>1,2</sup>

### Q. What is Cervilaxin?

A. Cervilaxin is a new, highly purified form of relaxin, a hormone normally produced at term.

### Q. When is it indicated?

A. Cervilaxin is of value in frank labor with slow cervical dilatation, and, with oxytocin, for induction of labor and uterine dysfunction.

### Q. What are its advantages?

A. Cervilaxin eases and shortens labor (see Fig. 1): less pain, less trauma, less need for intervention. It lessens danger of fetal damage (brain injury).

Cervilaxin makes oxytocin safer since there is less likelihood of uterine rupture or other adverse effects.

### Q. How does it act?

A. Cervilaxin softens the cervix so that it offers less resistance to passage of the fetus; dilatation is facilitated.

### Q. Is Cervilaxin recommended for controlling premature labor?

A. No. In massive doses Cervilaxin may retard uterine contractions and prevent premature birth, but this effect is not evident in the smaller doses recommended here.

### Q. Is Cervilaxin indicated only in primiparas?

A. No, Cervilaxin has been used with good results in primiparas, and in multiparas with a history of previous difficult labor.

### Q. Does Cervilaxin interfere with necessary uterine contractions during labor?

A. No. In recommended dosage there is no interference with well established, regular and normal physiological functions before, during, or after delivery.

### Q. What effect does Cervilaxin have on other drugs given during delivery?

A. Cervilaxin does not interfere with the action of any of the drugs commonly employed before, during, or after delivery.

### Q. What side effects have been observed?

A. To date, none.

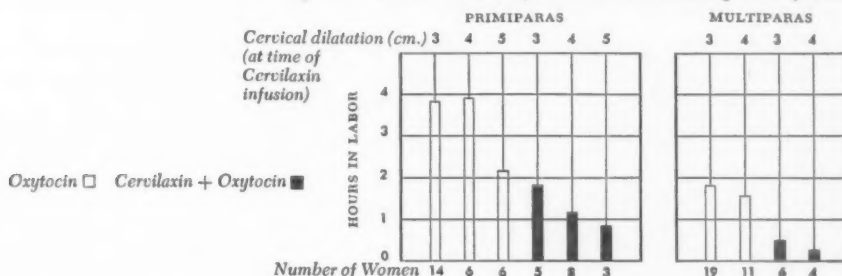
### Q. How is Cervilaxin administered?

A. By intravenous drip.

### Q. What is the dose?

A. Cervilaxin is supplied in 2 ml. vials containing 20 mg./ml. Usually this one dose is sufficient. Complete dosage and administration instructions are in the package literature.

Fig. 1. Time in labor—Oxytocin vs. Cervilaxin plus Oxytocin



1. Adapted from Birnberg, C. H. and Abitbol, M. M.: Refined Relaxin and Length of Labor, *Obst. & Gynec.*, in press.

2. Eisenberg, L.: Facilitation of Full-Term Labor with Relaxin, in press.

Products  
of Original  
Research



THE NATIONAL DRUG COMPANY  
Philadelphia 44, Pa.

CE-903/57

**MEAD JOHNSON**

SYMBOL OF SERVICE IN MEDICINE

throughout pregnancy and the postpartum

**the Colacero**

**for the management of constipation**

when bowel motility is adequate

**Colace**

Capsules  
Syrup  
Liquid (drops)

dioctyl sodium sulfosuccinate, Mead Johnson

**softens stools without laxative action**

By its surface-active properties, Colace increases the wetting efficiency of intestinal water and promotes formation of oil-water emulsions. Because it keeps stools soft for easy passage without laxative action and without adding bulk, Colace is especially valuable in pregnant and postpartum patients.



postpartum period

## eroducts Family

ent constipation

When bowel motility is inadequate

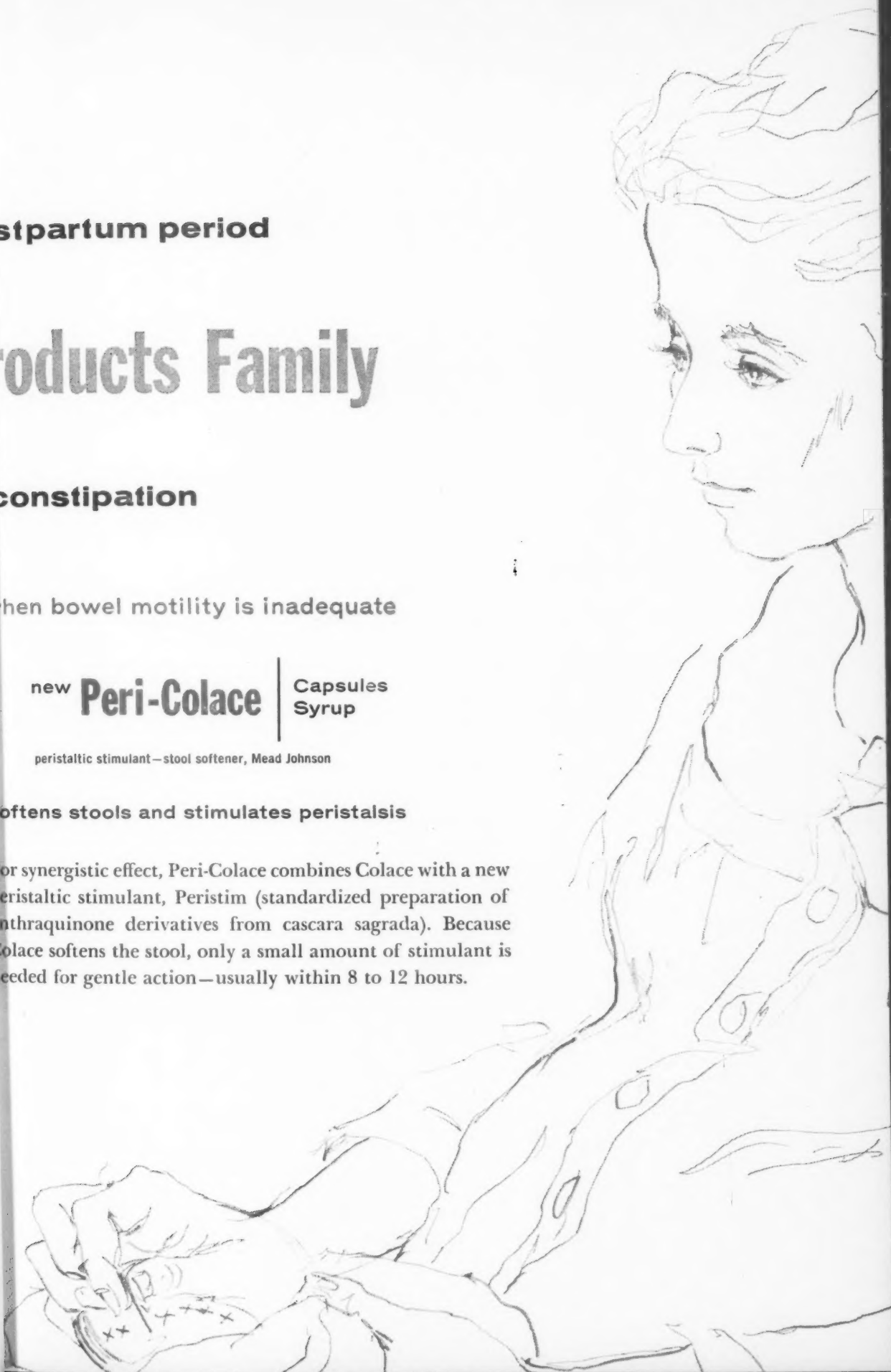
new **Peri-Colace**

Capsules  
Syrup

peristaltic stimulant—stool softener, Mead Johnson

softens stools and stimulates peristalsis

For synergistic effect, Peri-Colace combines Colace with a new peristaltic stimulant, Peristim (standardized preparation of anthraquinone derivatives from cascara sagrada). Because Colace softens the stool, only a small amount of stimulant is needed for gentle action—usually within 8 to 12 hours.





**HAPPY AGAIN...TODAY!**

# Trīva

*the modern time-saving treatment*

*for all three types of vaginitis*

In a matter of minutes... right after the first douche (today) ...Trīva helps relieve burning, itching and many other symptoms associated with vaginitis.

Trīva's powerful detergent surface-acting agent, plus a chelating agent, annihilates micro-organisms, almost instantly. Fact is, most cases of trichomonal and non-specific vaginitis are rendered asymptomatic in 2-5 days...organism-free within 12 days (monilia genus may require longer).

Trīva is safe, non-toxic, non-irritating...even during pregnancy...and will not stain clothing. Simple to prescribe: "Trīva (Boyle) sig; douche, b.i.d. for 12 days." For complete data, see PDR, 1958, pages 630, 631.

Full Treatment Package, literature on request. Write Dept. A2. Now available: color film "Management and Mismanagement of Breech Presentation."

AVAILABLE AT ALL PHARMACIES *in convenient packages of 24 individual 3 Gm. packets, each containing 35% Alkyl Aryl sulfonate (surface active and detergent), 0.33% Disodium ethylene bis-iminodiacetate (chelating agent), 53% Sodium sulphate, 2% Oxyquinoline sulfate and 9.67% dispersant.*

BOYLE

**BOYLE** & COMPANY LOS ANGELES 54, CALIF.

*Safety First*

## in control of Nausea of Pregnancy

The first thought of every physician during the prenatal period is the safety of the patient.

The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
2. EMETROL has been shown to be effective in nausea and vomiting in controlled clinical studies.<sup>1-3</sup>
3. EMETROL is so palatable that most patients will take it readily.
4. EMETROL works quickly, often bringing relief with the first dose.

SAFE

# EMETROL®

(Phosphorated Carbohydrate Solution)



1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.
2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

*Kinney*

KINNEY & COMPANY, INC.  
COLUMBUS, INDIANA





## RE-INFECTION CHECKMATE

"... the incidence of *Trichomonas vaginalis* in the male is the principal factor of re-infection in the female..."<sup>1</sup> The husband's cooperation, which often prevents a recurrence of the wife's infection, is readily gained when you make it a point to prescribe or recommend RAMSES® prophylactics. Specifying RAMSES for her husband when you outline therapy for your patient stresses the importance of his help as part of the treatment plan.

More husbands prefer RAMSES—the prophylactic with "built-in" sensitivity. These smooth, transparent, tissue-thin yet very strong prophylactics, made of natural gum rubber, are *different*. They do not dull sensation and are unexcelled in quality. You'll find that more husbands will cooperate with you in helping their wives if you remember to write or suggest RAMSES.

**RAMSES®**  
*prophylactics*



1. Feo, L. G., et al.: J. Urol. 75:711 (April) 1956.

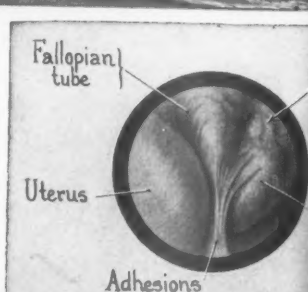
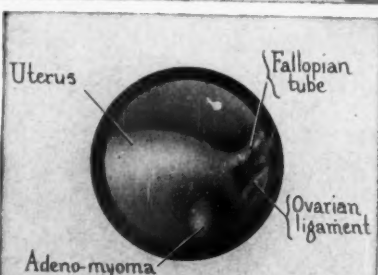
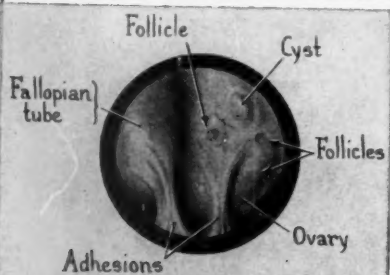
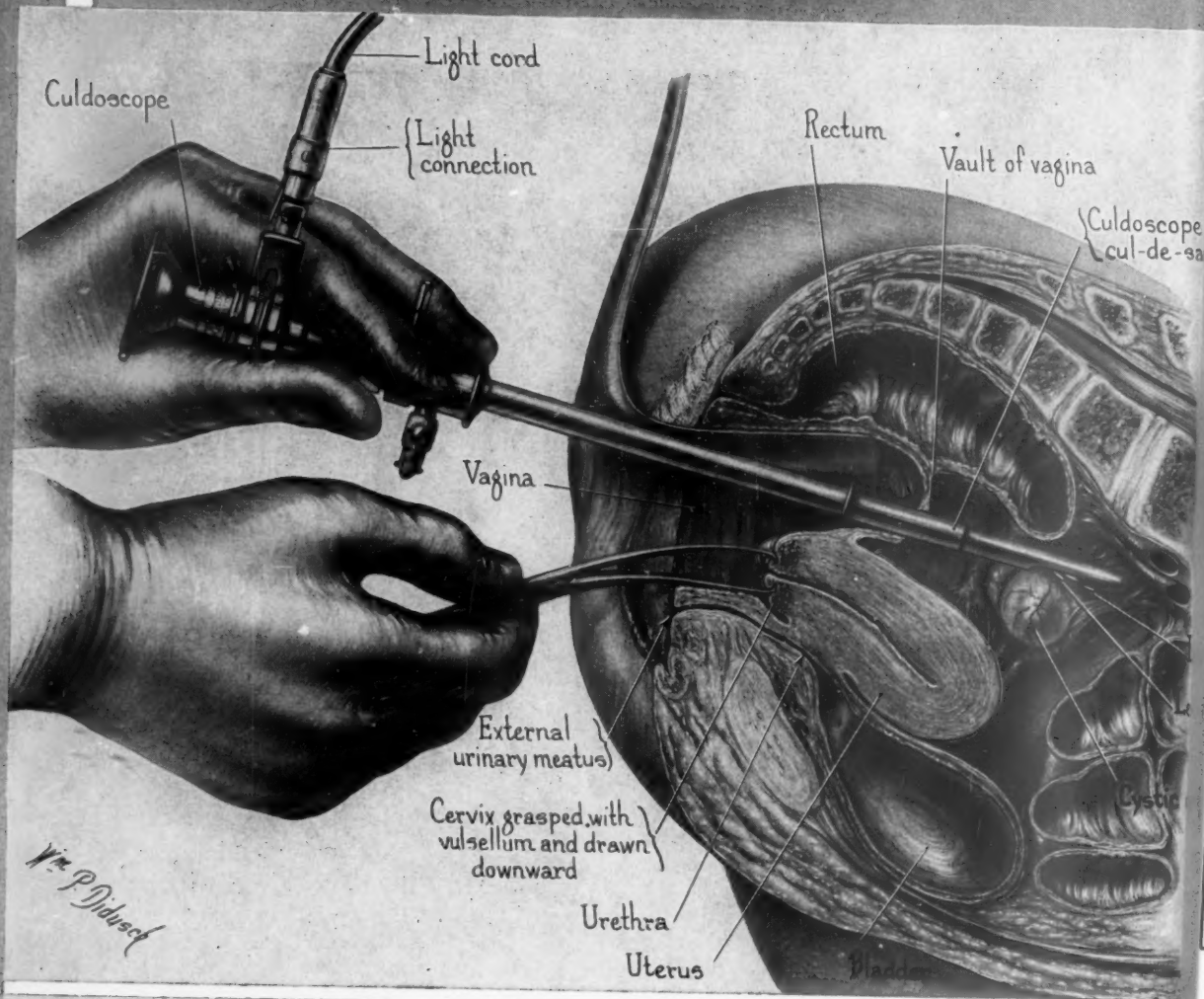
**JULIUS SCHMID, Inc.**  
423 West 55th Street  
New York 19, N.Y.

RAMSES is a registered trade-mark of Julius Schmid, Inc



*The Decker*

# CULDOSCOPE



The illustration above shows the Decker Culdoscope in endoscopic visualization of the female pelvic structures by the vaginal route. It permits direct study of pelvic tumors, ovarian pathologies, ectopic pregnancy, endometriosis, pelvic and intestinal adhesions, etc.

ESTABLISHED IN 1900



BY REINHOLD WAPPLER

FREDERICK J. WALLACE, President

*American Cystoscope Makers, Inc.*

8 PELHAM PARKWAY

PELHAM MANOR, N. Y.



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NU-MATI

Exclusive provide port, O. Criss-cross strain. Lig only 7 a extra cro

Nu-I

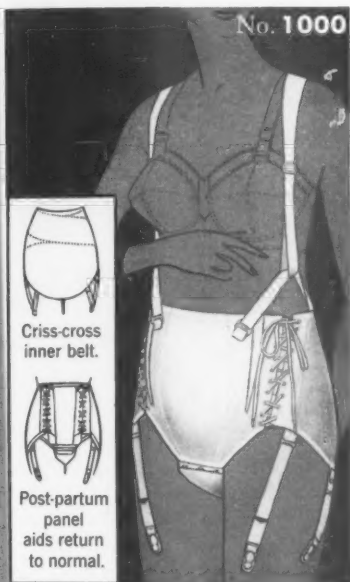
January,



**Nu-lift**

...for 20 years  
specialists in supports  
and bras for pregnancy

Scientific construction features provide for perfect fit and support during the many body changes throughout the entire term of pregnancy.



For relief from backstrain,  
vulva varicosities and  
pressure pains

**NU-LIFT Style No. 1000  
MATERNITY SUPPORT**

(Patent #2,345,760)

Exclusive patented shoulder straps provide natural "hammock" support, O-B front is adjustable. Criss-cross inner belt relieves back-strain. Light, comfortable, weighs only 7 oz. Post-natal front and extra crotch included.

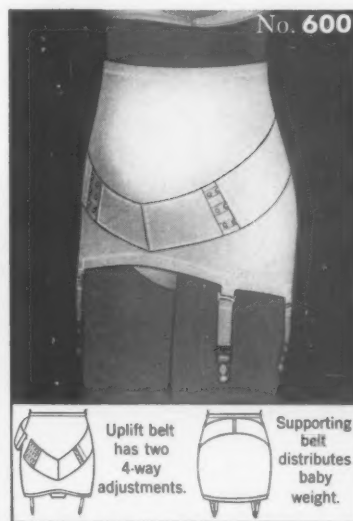
**Nu-lift**

1021 N. Las Palmas Ave.,  
Hollywood 38, California



**NU-LIFT Style No. 712  
MATERNITY  
and NURSING BRA**

Fully adjustable to allow for bust development during pregnancy. Unique drop-cup design for easy nursing. Inner half-cup gives healthful bust support. Fine broad-cloth stitched cup has inner lining of soft, absorbent flannelette to prevent irritation.



A "must" for  
every pregnancy

**NU-LIFT Style No. 600  
MATERNITY SUPPORT**

(Patent Pending)

Soft, elastic fabric gives comfortable support from third to ninth month, yet allows freedom and ease of movement. Wonderlift design supports back and baby without restricting. 4-position closure on each side to allow for development during entire term. Two removable crotch pieces for laundering ease, pantie protection.

Fill in and mail coupon below:

Nu-Lift Co., 1021 N. Las Palmas Ave., Hollywood 38, California  
Please send me full information on Nu-Lift Maternity  
Supports and Brassieres and free "Maternity Dates and  
Data" appointment booklet.

(PLEASE PRINT)

Dr.'s Name \_\_\_\_\_

Address \_\_\_\_\_

Practice: Obstetrics \_\_\_\_\_ Other \_\_\_\_\_

City \_\_\_\_\_ Zone \_\_\_\_\_ State \_\_\_\_\_

J 310-18



assure her


**a more serene, a happier pregnancy  
... without nausea**

give her **'MAREDOX'**<sup>®</sup> brand

Cyclizine Hydrochloride and Pyridoxine Hydrochloride

because

'Maredox' gives the expectant mother new-found relief from morning sickness.

*relieves nausea and vomiting  
and  
counteracts pyridoxine deficiency*  *in pregnancy*

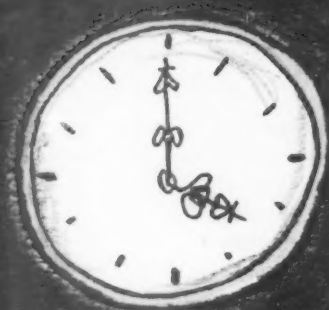
One tablet a day, taken either on rising or at night, is all that most women require.

Each tablet of 'Maredox' contains:

'Marezine' brand Cyclizine Hydrochloride . . . . . 50 mg.  
Pyridoxine Hydrochloride . . . . . 50 mg.



**BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York**



time cures  
colds and flu

while waiting,

**ROMILAR CF**

controls

the symptoms



as long as the cold or flu continues:

subdue the symptoms,

control the cough with

## ROMILAR CF

*The Complete Cold Formula*

ROMILAR CF brings new comfort and ease to your patients with colds and other upper respiratory disorders by providing more complete control of the symptom complex. It combines the benefits of an antihistamine, a decongestant and an analgesic-antipyretic with the effective cough suppressant action of Romilar Hydrobromide—the *non-narcotic* cough specific with codeine's antitussive effect but without codeine's side effects.

Available in syrup or capsule form. One teaspoonful (5 cc) of ROMILAR CF syrup, or one ROMILAR CF capsule, provides:

Romilar Hydrobromide (antitussive)	15 mg
Chlorpheniramine Maleate (antihistamine)	1.25 mg
Phenylephrine Hydrochloride (decongestant)	.5 mg
N-acetyl-p-aminophenol (analgesic-antipyretic)	120 mg

ROMILAR® Hydrobromide—  
brand of dextromethorphan hydrobromide



ROCHE LABORATORIES  
Division of Hoffmann-La Roche Inc.  
Nutley, New Jersey  
*Original Research in Medicine and Chemistry*





# rediscovered: the female urethra

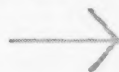
*newer knowledge of its structure and  
cytology provides a clearer understanding  
of its important role in pelvic distress.*

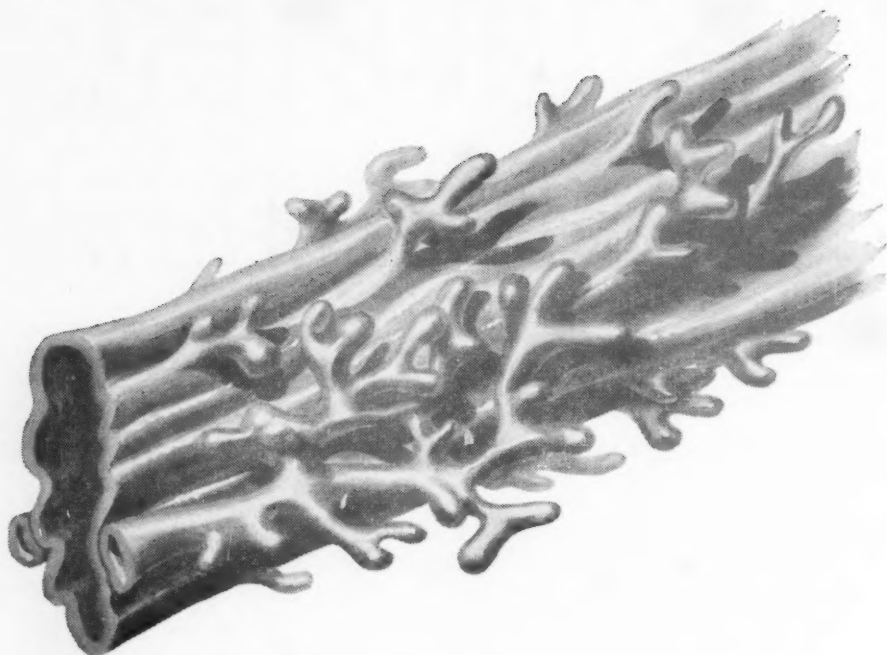


Schematic construction of female urethra demonstrating extensive network of peri-urethral glands, ending in numerous blind pockets. Drainage is into the urethra through small openings along its length, and into the para-urethral (Skene's) ducts.

## **1. Recent anatomic studies of the female urethra demonstrate a high susceptibility to infection.**

*A changing concept—The female urethra “was formerly considered only to be a short, simple, straight tube which served solely to empty the bladder. Recent studies have changed our notions concerning this . . . sections through the urethra and its surrounding tissues have shown numerous glands.”<sup>1</sup>*





Tortuous, with many interconnections but relatively poor drainage, these glands "form ideal foci for chronic infection."<sup>1</sup> Periurethral gland infection is followed by infiltration and thickening of the urethral wall, hypertrophy and granulation of the urethral mucosa, and constriction of the urethral lumen. The trauma of childbirth and coitus further invites infection of these delicate structures, which are exposed to vaginal and rectal discharges "from the period of diaper life to old age."<sup>1</sup> Thus, the urethra is not only a portal of entry for urologic infection, but the *site* of pathologic change "more frequently than any other portion of the female urinary tract."<sup>2</sup>

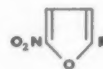
*Unrecognized source of pelvic symptoms*—Prevalent as it is in women, chronic urethritis "can be easily overlooked" because of the frequency with which the pain and discomfort are referred to other areas.<sup>2</sup> In addition to obvious urinary tract symptoms such as frequency, urgency, pain and burning on urination, chronic urethral infection is often responsible for pain in the lower abdomen and pelvis, lumbosacral region or upper thighs.

#### BACTERIAL URETHRITIS YIELDS QUICKLY TO

### **FURACIN<sup>®</sup>** *Urethral Suppositories*

brand of nitrofurazone

Insertion of these suppositories provides gentle dilation; the local anesthetic, dipiperdon, affords prompt and sustained relief of pain.<sup>3</sup> The antibacterial, FURACIN, achieves wide-spectrum bactericidal action without tissue toxicity. Each suppository contains FURACIN 0.2% and 2% dipiperdon • HCl in a water-dispersible base. Hermetically sealed in silver foil, box of 12.



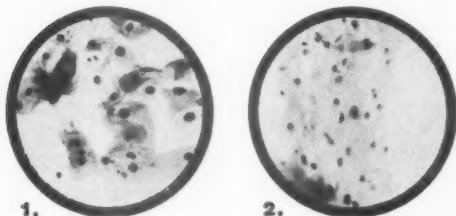
*The Nitrofurans—a unique class of antimicrobials . . . Products of Eaton Research*

## 2. Exfoliative cytology explains frequency of dyspareunia and other pelvic complaints in postmenopausal women.

*Senile urethritis: often encountered, seldom described*—A little known phenomenon has recently been reported by Youngblood and his colleagues.<sup>4,5</sup> Examining smears of epithelial cells from the urethrae of postmenopausal women, they found the same absence of normal, cornified, pyknotic squamous cells as in the vaginal smears, resulting from estrogen deficiency. Leukocytes and even erythrocytes were usually present, as in senile vaginitis. Along with these cytologic alterations, endoscopic examination revealed a hyperemic and atrophic urethral mucosa.

"Senile" urethritis is a common cause of dyspareunia, dysuria and other pelvic discomfort in postmenopausal women. Even when the urethra is recognized as the trouble spot, these women frequently fail to obtain relief because the underlying involutional nature of the urethritis is unsuspected, and antibacterial measures alone are employed. The lesion may resemble closely that of nonspecific urethritis.

*"Progressive histologic normalization" parallels rapid symptomatic relief with new Furestrol Suppositories.* In their investigations, Youngblood and co-workers<sup>4,5</sup> treated 120 postmenopausal, involutional urethritis patients with FURACIN Urethral Suppositories containing, in addition, 0.1 mg. of diethylstilbestrol. All showed prompt alleviation of symptoms, with disappearance of endoscopic signs of irritation. After 1 to 2 weeks' treatment, the urethral smears returned to normal, indicating replacement of the atrophic mucosa with a healthy, stratified squamous epithelium. These FURACIN-estrogen suppositories are now available as FURESTROL Suppositories.



1. Pretreatment urethral smear of postmenopausal woman with senile urethritis. Basal cells with low nucleocytoplasmic ratio are predominant, with leukocytes and erythrocytes.

2. Urethral smear from same patient after 2 weeks' treatment with FURESTROL Suppositories. The cornified, squamous cells indicate a healthy, normal epithelium.

*Ingredients work together*—FURACIN eradicated the low grade infection commonly present, while the diethylstilbestrol corrected the atrophic tissue changes. The excellent clinical results achieved with FURESTROL Suppositories could not be approached in control groups treated with suppositories from which any of the ingredients—FURACIN, estrogen, or dipherodon, the local anesthetic—had been eliminated.

POSTMENOPAUSAL URETHRITIS YIELDS PROMPTLY TO

## NEW FURESTROL<sup>T.M.</sup> Suppositories

Provides estrogen to reverse the involutional changes of senile urethritis, plus the antibacterial, anesthetic and gently dilating action of the FURACIN Urethral Suppository. Each FURESTROL Suppository contains FURACIN 0.2%, dipherodon·HCl 2%, and diethylstilbestrol 0.0077% (0.1 mg.), in a water-dispersible base. Hermetically sealed in orchid foil, box of 12.

**REFERENCES:** 1. Wharton, L. R. in Campbell, M.: Urology, W. B. Saunders Company, Philadelphia and London, 1954, Vol. 2, p. 1390 et seq. 2. Barrett, M. E.: J. M. Ass. Alabama 26:144, 1956. 3. Youngblood, V. H.: J. Urol. 70:926, 1953. 4. Youngblood, V. H.; Tomlin, E. M., and Davis, J. B.: Senile urethritis in women, J. Urol. (in press). 5. Youngblood, V. H.; Tomlin, E. M.; Williams, J. O., and Kimmelstiel, P.: Exfoliative cytology of the senile female urethra, Tr. Southeast. Sect. Am. Urol. Ass. (in press).

EATON LABORATORIES



NORWICH, NEW YORK

## A "SENSE OF WELL-BEING" IS A WOMAN'S PRIVILEGE



Every woman who suffers in the menopause deserves "Premarin."

Relief from distressing symptoms is promptly obtained and a "sense of well-being" is an extra benefit of therapy.

"Premarin" presents the complete equine estrogen-complex. Has no odor, imparts no odor. Available as tablets or liquid.

### "PREMARIN"®

Conjugated estrogens (equine)

**in the menopause and  
the pre- and postmenopausal syndrome**



AYERST LABORATORIES • New York, N. Y. • Montreal, Canada

5644



in postmenopausal vaginitis  
in vaginal plastic surgery

ORTHO®

Dienestrol CREAM

vaginal estrogen therapy

builds vaginal epithelium





**AZOTREX is the only  
urinary anti-infective  
agent combining:**

- (1) the broad-spectrum  
antibiotic efficiency of  
**TETREX**—the original  
tetracycline phosphate  
complex which pro-  
vides faster and higher  
blood levels;
- (2) the chemothera-  
peutic effectiveness of  
sulfamethizole—out-  
standing for solubility,  
absorption and safety;
- (3) the pain-relieving  
action of phenylazo-  
diamino-pyridine HCl  
—long recognized as a  
urinary analgesic.

**control of urinary**  
*through comprehensive*

*Literature and clinical supply  
on request*



**LABORATORIES INC., SYRACUSE, NEW Y**

This unique formulation assures faster and more certain control of urinary tract infections, by providing comprehensive effectiveness against whatever sensitive organisms may be involved. Indicated in the treatment of cystitis, urethritis, pyelitis, pyelonephritis, ureteritis and prostatitis due to bacterial infection. Also before and after genitourinary surgery and instrumentation, and for prophylaxis.

*In each AZOTREX Capsule:*

TETREX (tetracycline phosphate complex).....125 mg.

Sulfamethizole .....250 mg.

Phenylazo-diaminopyridine HCl .....50 mg.

*Min. adult dose: 1 cap. q.i.d.*

# tract infections

tetracycline-sulfonamide-analgesic action

# zotrex

CAPSULES

But, Doctor,  
I'm just  
*dragging* around!

When your pregnant patient complains that she is always tired, unable to finish her routine chores and—perhaps—somewhat depressed, you will frequently find the gentle stimulation of

## **'DEXEDRINE'**

useful. Either the 'Spansule' capsule (taken in the morning for all-day support) or the tablet (useful for shorter "tired" periods) will replace the characteristic lethargy of pregnancy with a feeling of energy, optimism and well-being. Dexedrine\* (dextro-amphetamine sulfate, S.K.F.)—available as tablets, elixir and Spansule\* sustained release capsules—is made only by Smith Kline & French Laboratories, Philadelphia

\*T.M. Reg. U.S. Pat. Off.





But, Doctor,  
I'm so *grouchy*  
all the time!

When your pregnant patient complains that she is always grouchy, irritable and "on edge," you will frequently find the mood-ameliorating action of

### **'DEXAMYL'**

useful. Because it contains both Dexedrine\* (dextro-amphetamine sulfate, S.K.F.) and amobarbital, Dexamyl\* induces a feeling of calmness and good humor—an "almost miraculous return to normal temperament for the pregnant patient." Available as tablets, elixir and Spansule\* sustained release capsules, 'Dexamyl' is made only by Smith Kline & French Laboratories, Philadelphia

\*T.M. Reg. U.S. Pat. Off.

# Meat...

## and the Effect of Maternal Protein Intake on Weight and Length of the Newborn

For many years it has been considered axiomatic that the size of the newborn reflects the nutritional status of the mother. But it remained for Burke and associates<sup>1</sup> to quantify this relationship. They found that weight and length of the infant at birth were directly related to the protein content of the mother's diet during the gravid period.

Babies born of mothers who consumed 85 grams of protein daily (National Research Council recommendation) averaged 3 pounds more in weight and 7 cm. more in length than infants whose mothers consumed 45 grams or less of protein daily during pregnancy.

When undernutrition occurs and intake of protein is reduced beyond a certain point (as happens during wartime starvation), pregnancy itself may fail to occur, presumably because of cessation of the reproductive cycle.<sup>2</sup>

Meat affords an excellent means of contributing biologically effective protein to the diet of the gravid woman. Its protein provides the gamut of the amino acids in proportion paralleling those in the protein of human tissues. Meat also supplies valuable amounts of B vitamins and minerals essential to both mother and fetus.

Meat one or more times daily is recommended throughout the entire period of pregnancy.

1. (a) Burke, B. S., and Stuart, H. C.: in Handbook of Nutrition, ed. 2, American Medical Association, New York, The Blakiston Company, 1951, pp. 293-326. (b) Burke, B. S.; Harding, V. V., and Stuart, H. C.: J. Pediat. 23:50 (Nov.) 1943.

2. (a) Smith, C. A.: Am. J. Obst. & Gynec. 53:599 (Apr.) 1947. (b) Sydenham, A.: Brit. M. J. 2:159 (Aug. 3) 1946.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

A m e r i c a n   M e a t   I n s t i t u t e  
Main Office, Chicago...Members Throughout the United States





*In urinary-tract infections*

**HIGH TISSUE LEVELS**

**HIGH BLOOD LEVELS**

**LOW TOXICITY**

**SUSPENSION**

**TABLETS**

**SULFOSE<sup>®</sup>**

*Triple Sulfonamides, Wyeth  
(Trisulfapyrimidines: Sulfadiazine,  
Sulfamerazine, Sulfamethazine)*

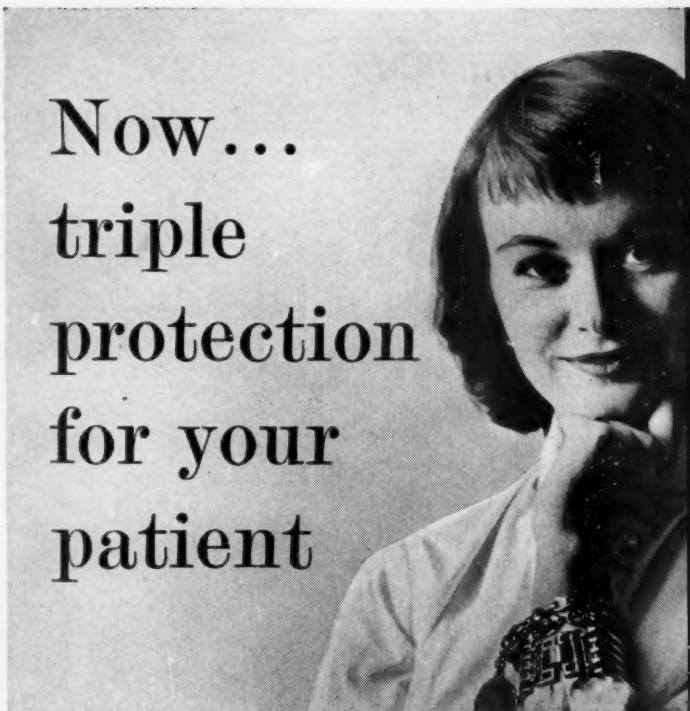


Philadelphia 1, Pa.

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.



Now...  
triple  
protection  
for your  
patient



CONTRACEPTIVE  
MONILIASTATIC  
TRICHOMONASTATIC

## LANTEEN® JELLY

*The preferred LANTEEN diaphragm and jelly technique of contraception affords extra benefits to patients susceptible to trichomonas reinfection and moniliasis. LANTEEN jelly is not only spermicidal, but also trichomonastatic and moniliastatic. No need to change to condom method. No extra cost.*

---

LANTEEN contraceptive jelly enables all your patients to use continuously the safest conception control method. Even your problem patients do not have to interrupt the diaphragm-jelly technique. The evident increase in the incidence of moniliasis suggests the use of a contraceptive that has been shown in the laboratory to be moniliastatic. Also, LANTEEN jelly's proven activity against trichomonas can aid in preventing reinfection with this organism by the male partner.

Write for complete details of LANTEEN's triple protection.

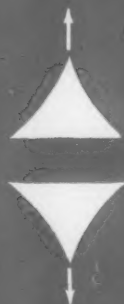
NOTE: LANTEEN JELLY IS NOT A TREATMENT FOR CLINICALLY ACTIVE MONILIASIS OR TRICHOMONIASIS

LANTEEN JELLY CONTAINS RICINOLEIC ACID 0.50%, HEXYLRESORCINOL 0.10%, CHLOROTHYMOL 0.0077%, SODIUM BENZOATE AND GLYCERIN IN A TRACACANTH BASE. DISTRIBUTED BY GEORGE A. BREON & COMPANY, 1450 BROADWAY, NEW YORK 18, N. Y. (IN CANADA: E. & A. MARTIN RESEARCH LTD., 20 RIPLEY AVE., TORONTO, CANADA) MANUFACTURED BY ESTA MEDICAL LABORATORIES, INC., CHICAGO 38, ILLINOIS.

*Prescribe LANTEEN JELLY for comprehensive conception control.*

a  
major  
advance  
in  
surgical  
needle  
design...

## NEW D & G ELLIPTRON\* NEEDLE



Regular and reverse cutting needles tend to "cut out" or cut too deeply.



New D & G ELLIPTRON Needle cannot "cut out" or "cut in"...makes smaller diameter hole.

## Combines Easy Penetration of Cutting Needle... Minimum Trauma of Taper Point

- Razor-sharp cutting point and new elliptical cross-section give easier initial penetration...then slip through tissue layers with greatly reduced trauma
- Cannot "cut out" or "cut in"...allows suturing close to wound edge for better tissue approximation
- Extra strength — elliptical shape provides maximum resistance to stress in any plane
- Greater stability in needle holder — will not slip...cutting edges cannot be damaged

D & G ELLIPTRON Needles,  $\frac{3}{8}$  circle, are now available in sizes suitable for plastic and gastrointestinal use, armed on Anacap® Silk and on Dermalon® Monofilament Nylon. A complete line of D & G ELLIPTRON Needle Sutures will be available shortly.

Producers of Davis & Geck Brand Sutures  
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Distributed in Canada by: North American Cyanamid Ltd., Montreal 16, P.Q.

\*Trademark Patent Pending

**CYANAMID**  
AMERICAN CYANAMID COMPANY  
SURGICAL PRODUCTS DIVISION  
DANBURY, CONNECTICUT



*you can give your  
patients "more potent"  
progestational therapy "with the  
advantage of a longer duration of action"*<sup>1</sup>

# DELALUTIN

Squibb Hydroxyprogesterone Caproate

## *longer-acting*

The A.M.A. Council on Drugs (formerly the Council on Pharmacy and Chemistry) points out that the indications for Delalutin are the same as those for progesterone, but Delalutin's prolonged action "makes it preferable to the parent drug in those conditions in which prolonged progestogen activity is desired."<sup>1</sup> A single injection provides your patients with sustained progestational activity for about 2 weeks, *simulating endogenous progesterone production.*

## *no definite contraindications*

The prolonged activity of Delalutin is useful in preventing abortion, habitual and threatened, due to progesterone inadequacy, and in restoring the manifestations of normal ovarian function in nonpregnant women. The A.M.A. Council further states: "The local and systemic toxic effects of hydroxyprogesterone caproate are minimal, and, in therapeutic doses, there are no definite contraindications to its use."<sup>1</sup> For dosage schedule, see package insert.

*2 cc. and 10 cc. vials, 125 mg. per cc.*

**SQUIBB**



*Squibb Quality—  
the Priceless Ingredient*

<sup>1</sup>. Council on Pharmacy and Chemistry: J. A. M. A. 163:356 (Feb. 2) 1957

<sup>1</sup>DELALUTIN® IS A SQUIBB TRADEMARK



# BONADOXIN<sup>®</sup>

## STOPS MORNING SICKNESS...BUT



## ...IT DOESN'T STOP THE PATIENT



...and for a nutritional buildup  
plus freedom from leg cramps\*

### STORCAVITE<sup>®</sup>

phosphate-free calcium, 10 essential  
vitamins, 8 important minerals.  
Bottles of 100.

\*due to calcium-phosphorus imbalance



NEW YORK 17, NEW YORK  
Division, Chas. Pfizer & Co., Inc.

BONADOXIN brings relief to 88.1%  
of patients...often within a few hours.<sup>1,2</sup>  
But it does not produce drowsiness, or  
side effects associated with over-potent  
antinauseants. With safe BONADOXIN,  
"toxicity and intolerance...[is] zero."<sup>2</sup>

Is she blue at breakfast? Prescribe  
BONADOXIN. Usually just one tablet at  
bedtime stops nausea and vomiting  
of pregnancy...

and just one supplies the  
full 50 mg. of pyridoxine. ←

EACH TABLET CONTAINS:

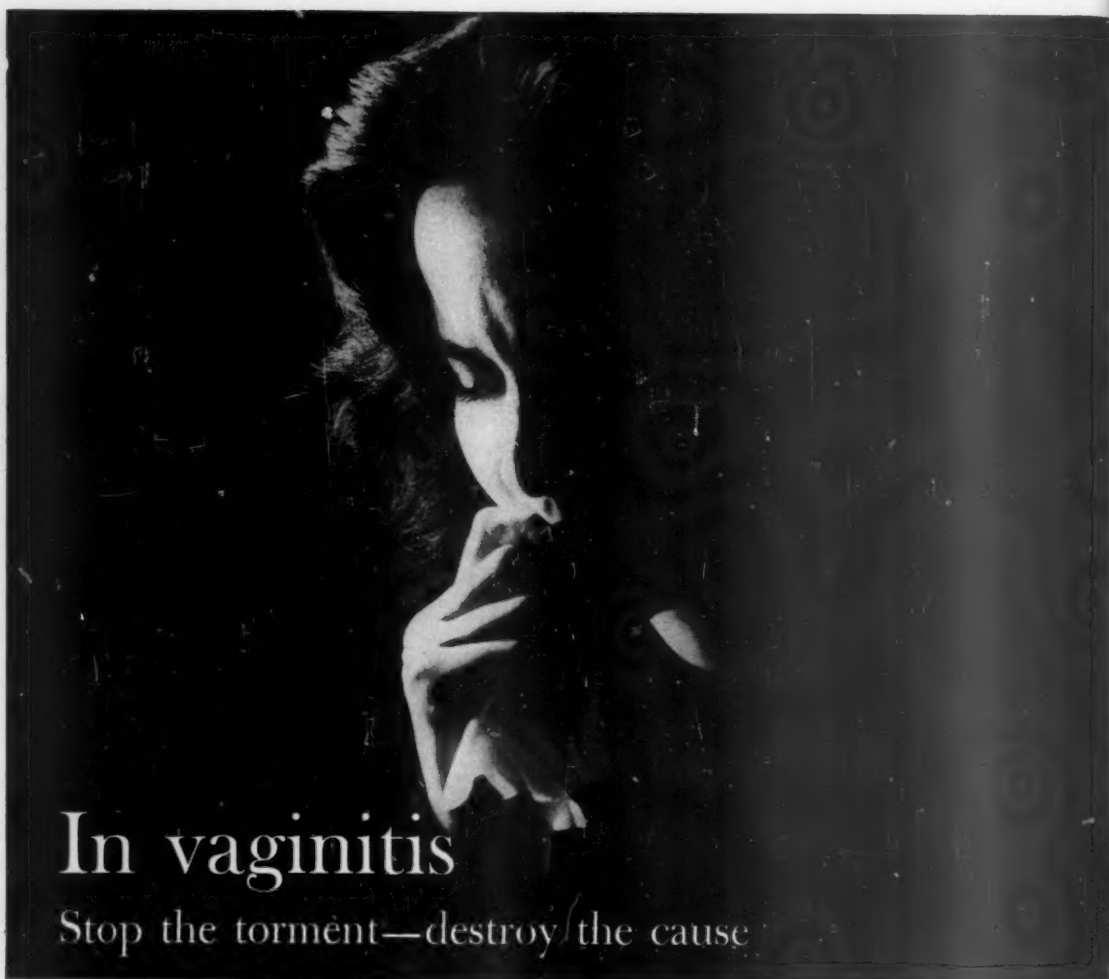
MECLIZINE HCl..... 25 mg.

PYRIDOXINE HCl..... 50 mg.

Bottles of 25 and 100.

References: 1. Groskloss, H. H., et al: Clin.  
Med. 2:885 (Sept.) 1955. 2. Goldsmith, J. W.:  
Minnesota Med. 40:99 (Feb.) 1957.





# In vaginitis

Stop the torment—destroy the cause

# AVC

*Improved*



**in trichomonal vaginitis —**

*"... the most effective treatment available."<sup>1</sup>*



**in monilial vaginitis —**

*"... more effective than any other agent ... used previously."<sup>2</sup>*



**in mixed infection —**

*"... the most effective treatment of endocervicitis. . . ."<sup>3</sup>*

Products of  
Original Research



**THE NATIONAL DRUG COMPANY**  
Philadelphia 44, Pa.

The rate of cure with AVC Improved is consistently high in all common types of vaginitis. In one series of patients with trichomonal vaginitis, bacteriologic cures were obtained in 82.5% of the cases.<sup>1</sup> Symptomatic relief is rapid and lasting. And because AVC Improved has an acid pH, it encourages the early return of normal vaginal flora.

**Composition:** A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

**Indications:** Trichomonal leukorrhea; monilial and nonspecific vaginitis; cervicitis; postpartum hygiene; pre- and postcauterization, coagulation, conization, and other vaginal surgery; vaginal infections in children.

**Administration:** An applicatorful twice daily—on arising and at bedtime.

**Supplied:** 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. 2:45, 1955. (2) Hensel, H. A.: Postgrad. Med. 8:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

Most effective when used preoperatively

# Adrenosem<sup>®\*</sup>

SALICYLATE  
(Brand of carbazochrome salicylate)

to control oozing and bleeding

As one clinician states: "Blood loss may be hidden temporarily after closure of the thoracic or abdominal cavities, even though drains are in place. Obstruction to outflow through these drains can occur, and bleeding is not apparent.

"There are certain clinical situations in which prolonged and profound oozing of blood may occur."<sup>1</sup>

Published reports<sup>2-6</sup> over the last five

years emphasize the value of Adrenosem preoperatively—to control oozing and bleeding and provide a clearer operative field.

Adrenosem does not affect blood pressure, cardiac rate or output, blood clotting mechanism, massive hemorrhage, or arterial bleeding.<sup>7</sup>

*Supplied in ampuls,  
tablets and as a syrup.*

\*U.S. Pat. 2581850, 250629

**THE S. E. MASSENGILL COMPANY**

BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

One of the many procedures where

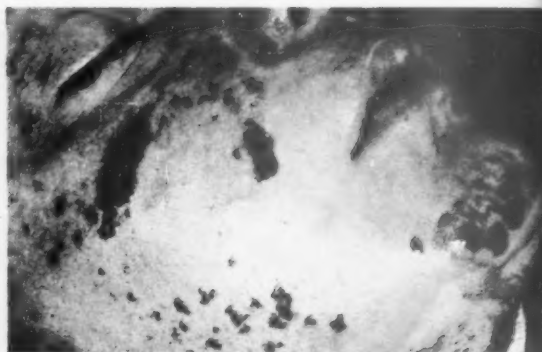
**Adrenosem<sup>®</sup>**  
SALICYLATE

has been especially effective when used preoperatively

The photographs below are of two typical cases in 200 dermabrasion procedures<sup>4</sup> over a period of two years.



Case #1 Left cheek untreated



Case #1 Right cheek, after treatment with Adrenosem



Case #2 Left cheek untreated



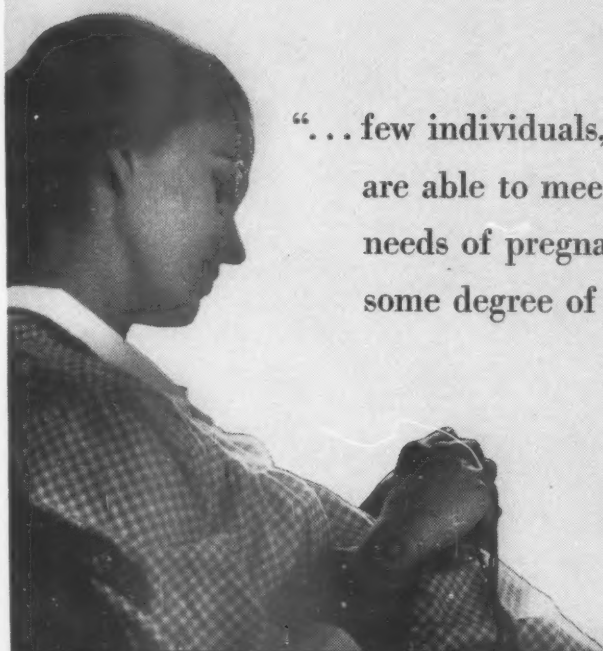
Case #2 Right cheek, after treatment with Adrenosem

Write for literature describing the action and uses of Adrenosem Salicylate

## THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

1. Dripps, R.D.: Hazards of the Immediate Postoperative Period, J.A.M.A. 7:795 (Oct. 19, 1957) [This reference reviews postoperative hazards, and does not refer to Adrenosem Salicylate]
2. Ersner, M.S., and Lerner, S.S.: M. Clin. North America 40:1749 (Nov., 1956)
3. Peele, J.C.: Further Observations on the Use of Adrenosem Salicylate in the Control of Hemorrhage from the Nose and Throat, N. Carolina M.J. 17:98 (March, 1956)
4. Brown, W.S.: The Use of Adrenosem Salicylate to Control Postoperative Bleeding in Plastic Surgery Dermabrasion, Northwest Medicine. In Press.
5. Wilkins, B.D.: Gastrointestinal Bleeding as Seen by the Proctologist, J.A.M.A. 163:1214 (April 6, 1957)
6. Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N. State J. Med. 55:886 (Mar., 1956)
7. N.N.R., 1957, p. 265



"... few individuals, if any,  
are able to meet the increased  
needs of pregnancy without suffering  
some degree of deprivation."<sup>1</sup>

Help assure your patients  
nutritionally perfect pregnancies  
prescribe

# Engran

Squibb Vitamin—Mineral Supplement

just 1 small capsule-shaped tablet daily

Each small capsule-shaped tablet provides:

Vitamin A	5,000 U.S.P. Units
Vitamin D	500 U.S.P. Units
Vitamin K (as menadiolone)	0.5 mg.
Thiamine Mononitrate	3 mg.
Riboflavin	3 mg.
Pyridoxine HCl	2 mg.
Vitamin B <sub>12</sub> Activity Concentrate	2 mcg.
Folic Acid	0.25 mg.
Niacinamide	20 mg.
Calcium Pantothenate	5 mg.
Ascorbic Acid	75 mg.
Calcium, elemental (as calcium carbonate, 375 mg.)	150 mg.
Iron, elemental (as ferrous sulfate exsiccated, 33.6 mg.)	16 mg.
Iodine, elemental (as potassium iodide, 0.2 mg.)	0.15 mg.
Potassium (as the sulfate)	5 mg.
Copper (as the sulfate)	1 mg.
Magnesium (as the oxide)	6 mg.
Manganese (as the sulfate)	1 mg.
Zinc (as the sulfate)	1 mg.

"ENGRAN" and "TERM-PAK" are SQUIBB TRADEMARKS

## Supply

Bottles of 100 and 1000. For  
your patient's convenience,  
*Engran Term-Pak* provides  
250 tablets—enough to last  
until term—in a handsome re-  
usable glass jar plus a purse-  
size dispenser.



Reference: 1. Tompkins, W. T. in Wohl,  
M. G. and Goodhart, R. S.: *Modern Nutri-  
tion in Health and Disease*, Lea & Febiger,  
Philadelphia, 1955, p. 886.

## Advantages

- specifically formulated for the  
mother-to-be
- generous amounts of 11 vitamins  
and 8 minerals
- contains vitamins A, C, D, K and  
the B complex
- provides phosphorus-iron-calcium,  
plus iron and trace elements

SQUIBB



*Squibb Quality—the Priceless Ingredient*





IN



PATIENT



AFTER



PATIENT

## ARMOUR thyroid

unsurpassed in quality and  
for consistent therapeutic  
results.

### Indicated in

myxedema and other frank thy-  
roid deficiencies  
when hypothyroidism is involved

chronic recurrent colds  
postpartum fatigue  
functional menstrual disorders  
sterility  
habitual abortion  
certain anemias  
obesity  
hypometabolism

No other thyroid product has been used so widely and so often by  
leading physicians everywhere. On your prescriptions *specify*  
ARMOUR Thyroid.



**THE ARMOUR LABORATORIES**

A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS



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ILLINO  
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# FOR SUPERIOR CONTROL OF ACUTE AND CHRONIC URINARY TRACT INFECTIONS

**TERRAMYCIN<sup>®</sup>** established  
agent  
of choice

BRAND OF OXYTETRACYCLINE      CAPSULES, 250 mg., 100 mg. and 50 mg.

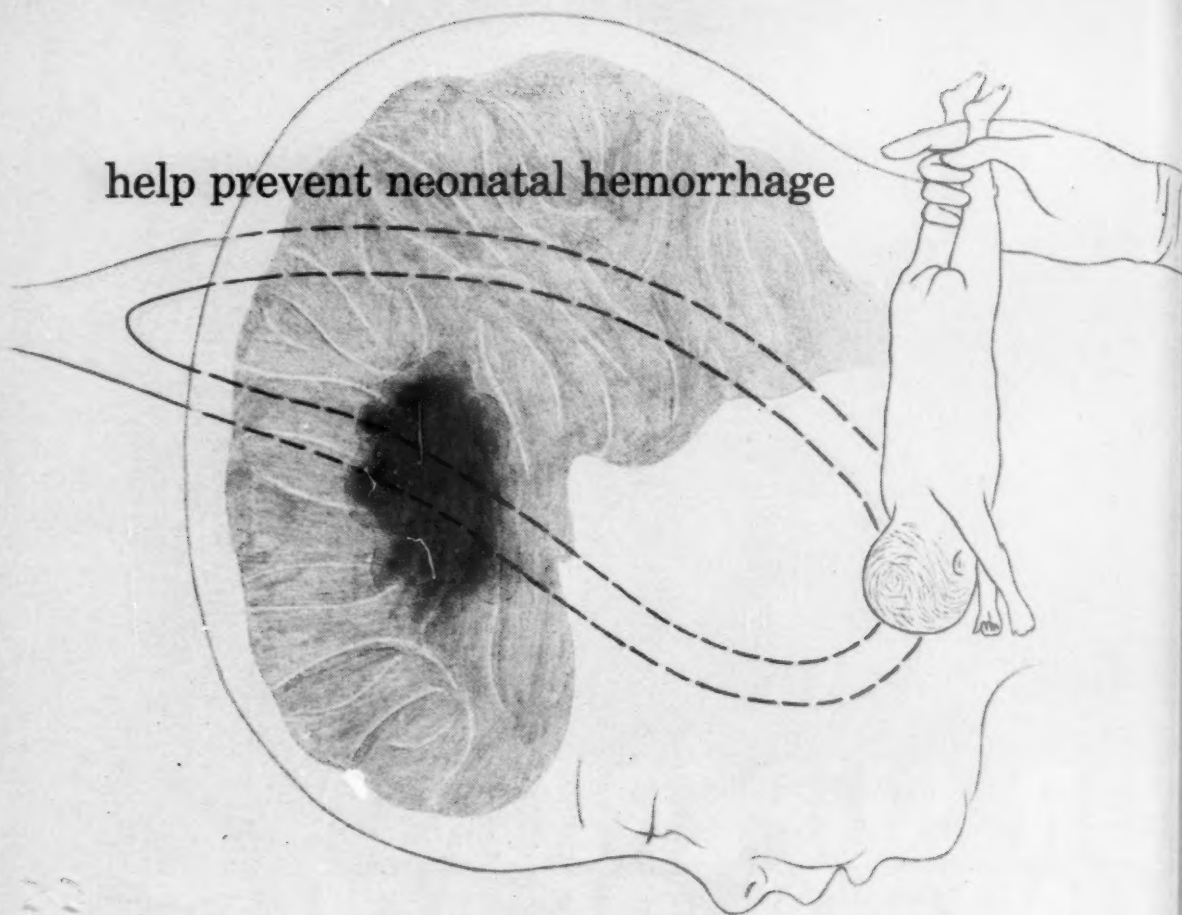
Terramycin "... is an antibiotic of proved worth in the treatment of infections of the genitourinary tract. It has the advantage of a wide range of antibacterial effectiveness without the disadvantage of toxicity or side reactions."<sup>1</sup>



PFIZER LABORATORIES  
Division, Chas. Pfizer & Co., Inc.  
Brooklyn 6, N. Y.

<sup>1</sup>Haum, W. C.: Internat. Rec. Med. 168:248 (April) 1955.

help prevent neonatal hemorrhage



# MEPHYTON<sup>®</sup>

VITAMIN K<sub>1</sub>

*the only available preparation chemically identical with naturally-occurring vitamin K<sub>1</sub>  
"has a more prompt, more potent and more prolonged effect than the vitamin K analog"*

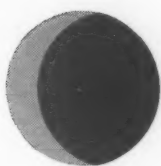
- helps prevent "physiologic" hypoprothrombinemia, the most probable cause of hemorrhagic disease of the newborn
- helps reduce incidence of intracranial hemorrhage at birth
- if 'Mephyton' has not been given to the mother before delivery, it can be administered to the infant if birth is premature, if surgery is necessary, or if treatment of neonatal hemorrhage is required

**Dosage:** Hemorrhagic disease of the newborn, 0.5 to 2 mg. prophylactically to the mother is usually adequate; if actual hemorrhage occurs, up to 10 mg., repeated if necessary, may be given to the newborn.

**Supplied:** Tablets, 5 mg., bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg., boxes of 6 ampuls.




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while the patient sleeps

# agoral<sup>®</sup>

vanilla-flavored laxative

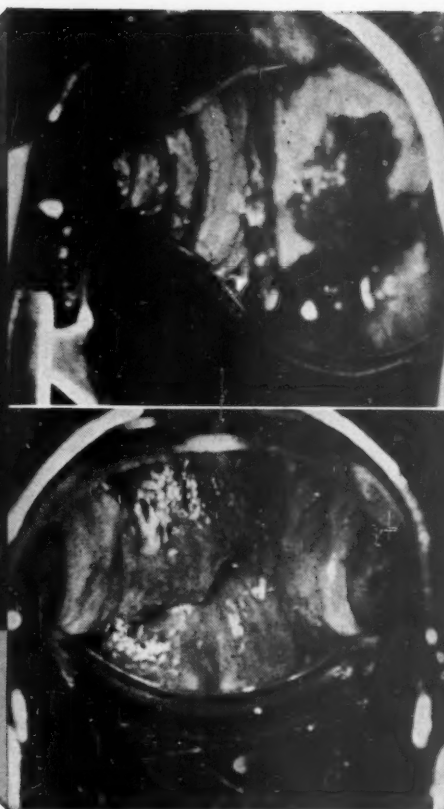


works gently  
to produce a normal  
bowel movement  
in the morning.

Dosage: One tablespoonful at bedtime

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WHEN YOU  
WANT EXCELLENT  
RESULTS IN  
MONILIAL  
VAGINITIS



# MYCOSTATIN

## VAGINAL TABLETS

Squibb Nystatin

### RESULTS:

"Of 96 patients with records suitable for tabulation, 85 had from good to excellent results."<sup>1</sup> In a group of 13 pregnant and 12 nonpregnant clinic patients "all patients were rapidly relieved of their symptoms, within 24 hours in most cases. . . . The writer has seldom been so rapidly convinced of the value of a new therapeutic agent."<sup>2</sup>

Mycostatin is the safe, highly effective antifungal antibiotic . . . with direct, specific action against monilia. When you use Mycostatin Vaginal Tablets for your patients with monilial vaginitis, your therapy can be 98.3% successful.<sup>3</sup> And your treatment will be clean—without messiness or staining—a point your patients will appreciate.

Each tablet contains 100,000 units of Mycostatin and 0.95 Gm. lactose. Packages of 15 with applicator; packages of 100 without applicator. Each tablet individually foil wrapped.

**Therapy:** 1 tablet intravaginally once to twice daily for 2 weeks, or as required.

You can also use Mycostatin Oral Tablets; Mycostatin Ointment; Mycostatin Dusting Powder; Mycostatin for Suspension.

1. Thomas, H. H.: *Obstet. & Gynec.* 9:163, 1957. 2. Browne, A. D. H.: *J. Irish M.A.* 40:86, 1957. 3. Pace, H. R., and Schantz, S. I.: *J.A.M.A.* 162:268, 1956.

\*MYCOSTATIN® IS A SQUIBB TRADEMARK

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SQUIBB QUALITY—  
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extra protection for every conception



*Decidual bleeding due  
to capillary fragility  
leads to abortion*

# Hesper-C Prenatal

*with capillary-protective factors plus vitamins-minerals*

*a precaution in every pregnancy*

*a necessity in habitual abortion<sup>1,2</sup>*

Routine care during pregnancy should include protection against decidual bleeding. To guard against spontaneous and habitual abortion, Hesper-C Prenatal provides the essential capillary-protective factors (hesperidin complex and ascorbic acid) *plus* the supplemental vitamins and minerals required during gestation.

*The usual daily dosage (2 capsules t.i.d.) provides:*

HESPERIDIN COMPLEX .....600 mg.  
ASCORBIC ACID .....600 mg.  
Ferrous Gluconate (15 mg. iron) .....130 mg.  
Calcium Pantothenate .....6 mg.  
Calcium Carbonate (500 mg. calcium) .....1.25 Gm.  
Vitamin A Acetate .....6,000 U.S.P. Units  
Vitamin D<sub>2</sub> .....1,200 U.S.P. Units

Thiamine Mononitrate .....7.5 mg.  
Riboflavin .....4.5 mg.  
Nicotinamide .....30.0 mg.  
Vitamin B<sub>12</sub> .....4.5 mcg.  
Folic Acid .....0.3 mg.  
Pyridoxine Hydrochloride .....10.0 mg.  
Copper Sulfate (3.0 mg. copper) .....12.0 mg.  
Potassium Iodide (0.3 mg. iodine) .....0.4 mg.

Providing the daily requirements or more of vitamins and iron during pregnancy as recommended by the National Research Council.

1. Greenblatt, R. B.: *Obst. & Gynec.* 2:530, 1953.

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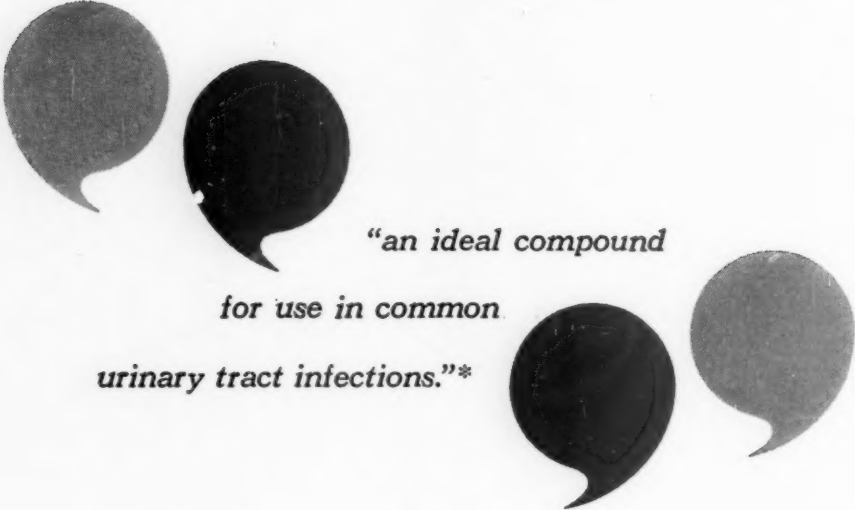
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HCP 1800/57

January, 1958

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\*F. K. Garvey and J. M. Lancaster, North Carolina M. J., 18:78, 1957.

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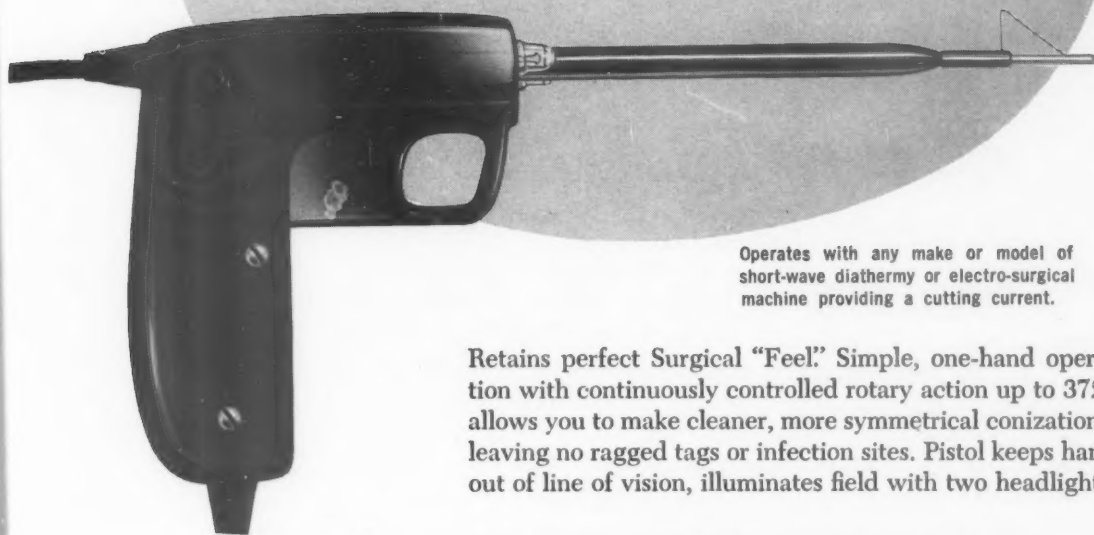
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REFERENCES

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5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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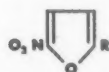
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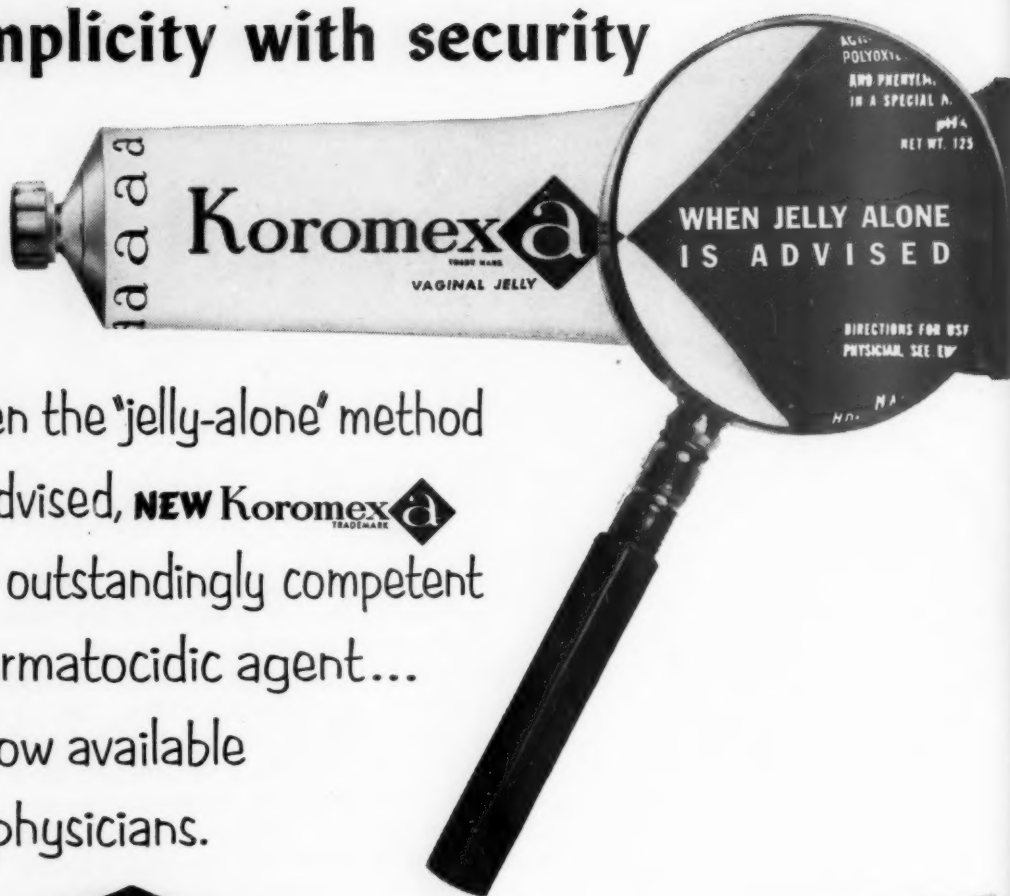
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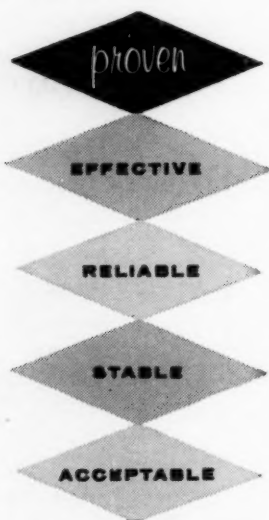


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"Extraordinarily well tolerated" in 120 obstetrical and gynecological patients.<sup>2</sup>

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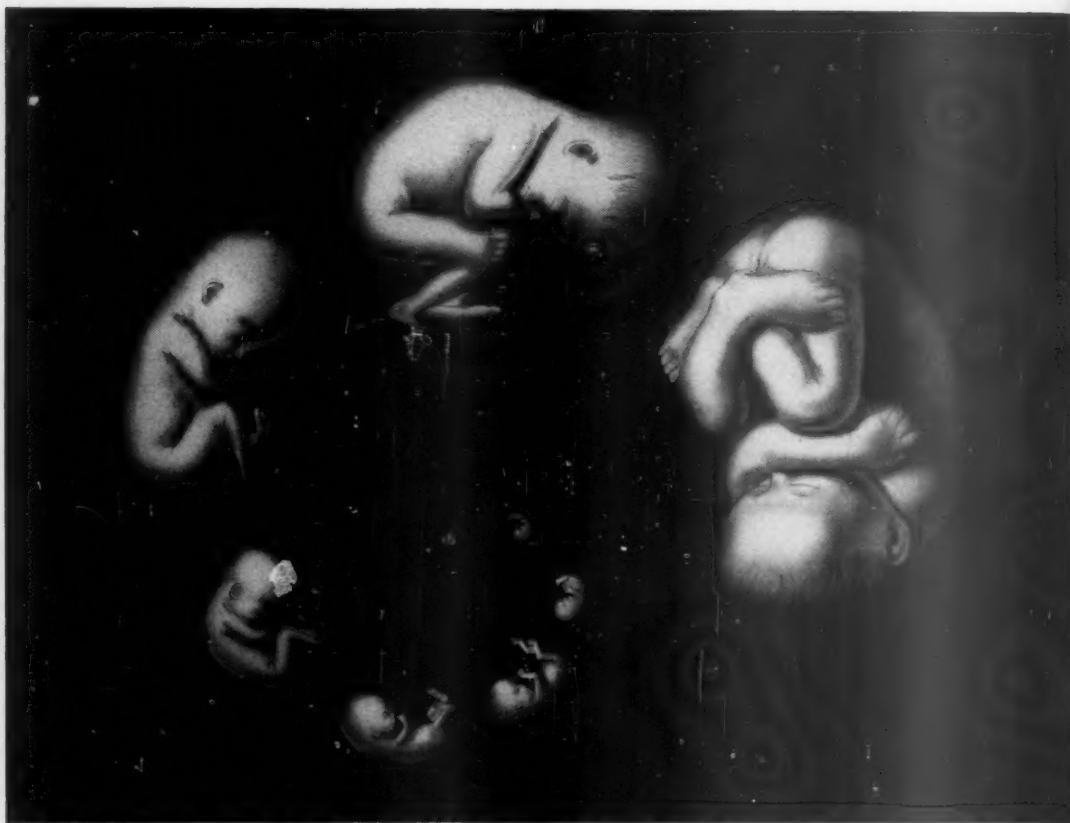
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**A complete prenatal supplement.** Designed for routine use throughout pregnancy, Calcisalin assures important vitamin and mineral benefits. The daily dose provides

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**Provides usable calcium.** Recent evidence indicates that phosphate-containing supplements can actually cause

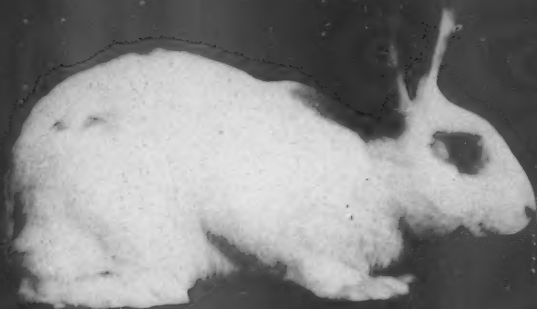
calcium blood levels to fall.<sup>1-5</sup> However, Calcisalin supplies calcium in the *usable* form of the lactate salt. To absorb excess dietary phosphorus, Calcisalin also provides reactive aluminum hydroxide gel. Thus the risk of inadvertently raising the phosphorus level to the point where it interferes with calcium absorption is avoided.

**Dosage:** Two tablets three times daily after meals. Available: Bottle of 100 tablets and 8-oz. reusable nursing bottles containing 300 tablets.

**References:** 1. *Obst. & Gynec.* 7:94 (Jan.) 1953. 2. *Illinois M. J.* 105:305 (June) 1954. 3. *Bull. Margaret Hague Maternity Hosp.* 6:107 (Dec.) 1953. 4. *Missouri Med.* 51:727 (Sept.) 1954. 5. *J. Michigan M. Soc.* 53:862 (Aug.) 1954.

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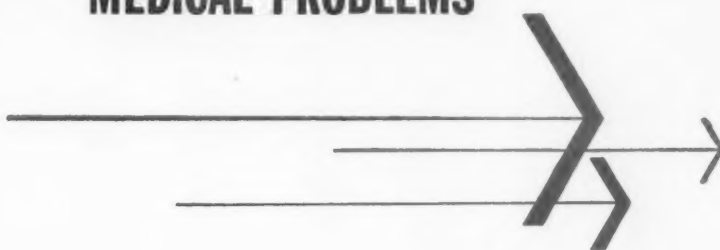


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# Edema and Hypertension

## EDEMA

1. 'DIURIL' is an entirely new, orally effective, nonmercurial agent—1 Gm. of 'DIURIL' orally being approximately equivalent to 1 cc. of mercurial I.M.
2. 'DIURIL' is ideal for initiating diuresis and for prolonged maintenance of the edema-free state.
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**any indication for diuresis  
is an indication for 'DIURIL'**

INDICATIONS: Congestive heart failure; premenstrual edema; edema of pregnancy; renal edema—nephrosis, nephritis; cirrhosis with ascites; drug-induced edema. May be of value to relieve fluid retention complicating obesity.

DOSAGE RANGE: one 500 mg. tablet 'DIURIL' to two 500 mg. tablets 'DIURIL' once or twice a day.

SUPPLIED: 250 mg. and 500 mg. scored tablets of 'DIURIL' (Chlorothiazide); bottles of 100 and 1,000.

BIBLIOGRAPHY: Baer, J. E. et al.: *Fed. Proc.* **16**:278, (March) 1957; Beyer, K. H. et al.: *Fed. Proc.* **16**:282, (March) 1957; Ford, R. V. et al.: *M. Rec. & Ann.* **51**:376, (April) 1957; Ford, R. V. et al.: *Arch. Int. Med.* **100**:582, (October) 1957; Ford, R. V. et al.: *Antibiotic Med. & Clin. Therapy* (in press); Moyer, J. H. et al.: *Proc. Soc. Exper. Biol. & Med.* **95**:529, (July) 1957; Novello, F. C. and Sprague, J. M.: *J. Am. Chem. Soc.* **79**:2028, (April 20) 1957; Russo, H. F. et al.: *Fed. Proc.* **16**:333, (March) 1957; Hollander, W. and Wilkins, R. W.: *Boston Med. Quart.* **8**:69, (Sept.) 1957; Freis, E. D. et al.: *J.A.M.A.* (in press); Finnerty, F. A.: *N. Y. State J. Med.* **57**:2957, (Sept. 15) 1957; Freis, E. D. and Wilson, I. M.: *Med. Ann. District of Columbia* **26**:468, (Sept.) 1957; Freis, E. D. et al.: *Circulation* (in press).

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Hyoscyamine Sulfate.....0.1037 mg.  
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Tetracycline (phosphate-buffered) and Nystatin

Combines ACHROMYCIN<sup>†</sup> V with NYSTATIN

ACHROSTATIN V combines ACHROMYCIN<sup>†</sup> V...  
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ACHROSTATIN V CAPSULES  
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**References:** 1. Wolff, J. R.: In press. 2. Ray, J. L., and Maughan, G. M.: West. J. Surg. 64:581 (Nov.) 1936. 3. Feldman, R. L.: In press. 4. Hoefler, W. H. W.; Bailey, F. A., and Farley, W. W.: Antibiotic Med. & Clin. Therapy 4:31 (Jan.) 1957. 5. Gardiner, H. L., and Dukes, C. D.: J. Obst. & Gynec. 69:962 (May) 1955.

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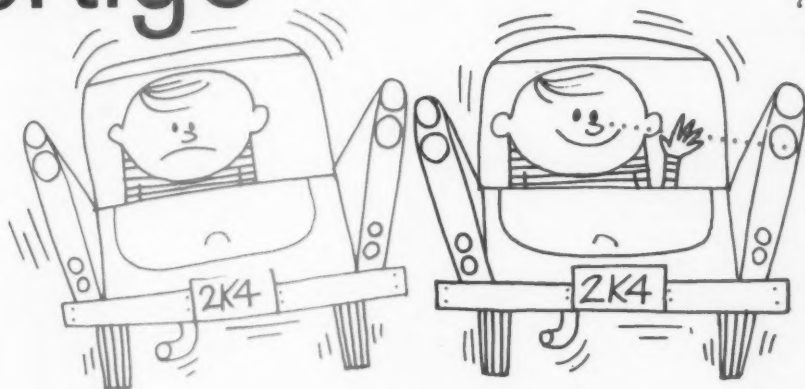


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1. Semmens, J. P.: *Obst. & Gynec.* 9:586  
(May) 1957. 2. Conner, P. K., and Moyer,  
J. H.: *GP* 14:124 (Nov.) 1956. 3. Charles,  
C. M.: *Geriatrics* 2:110 (March) 1956.

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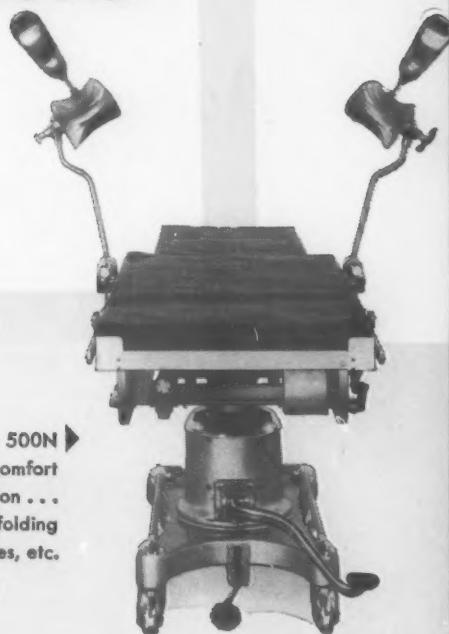
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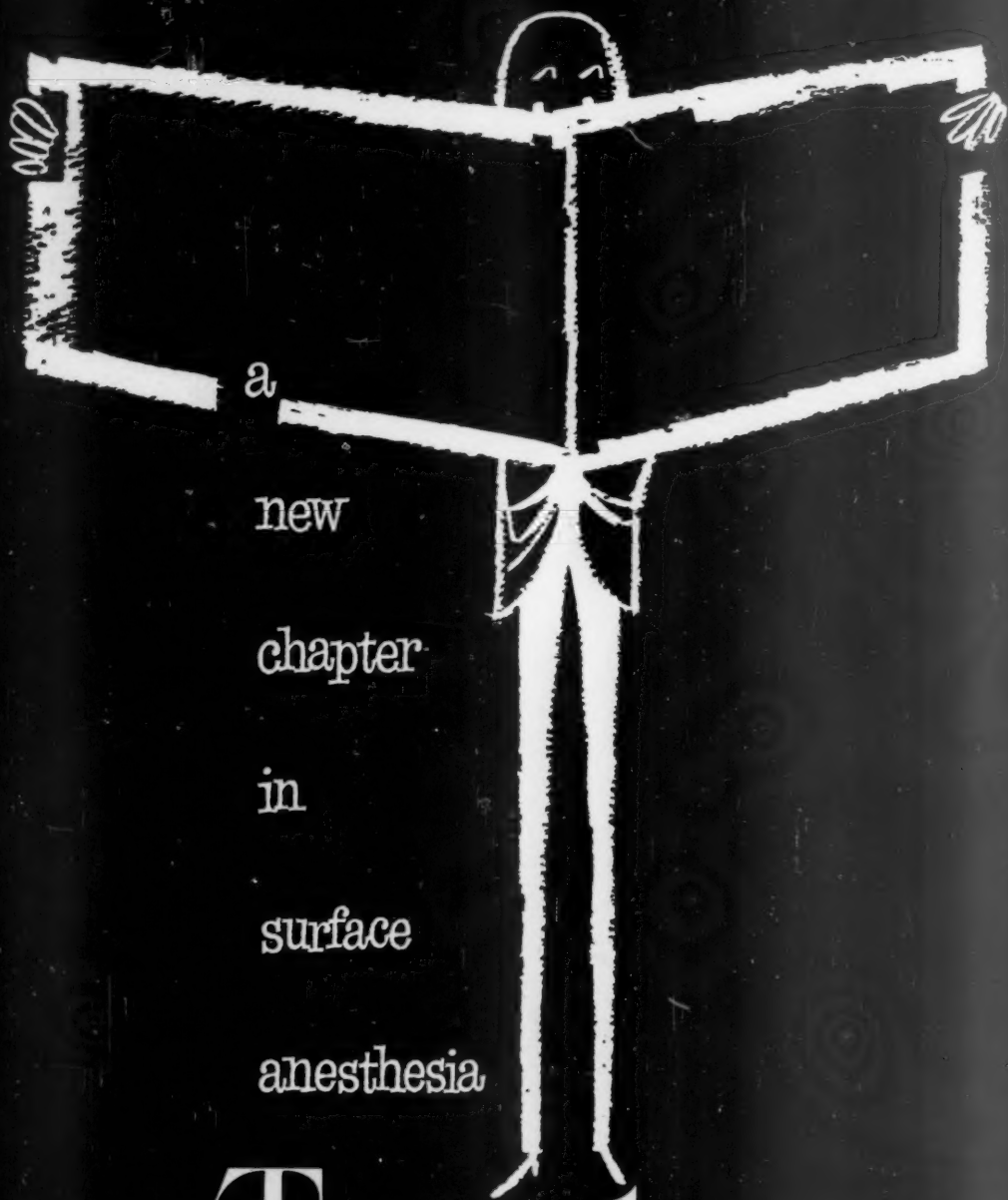
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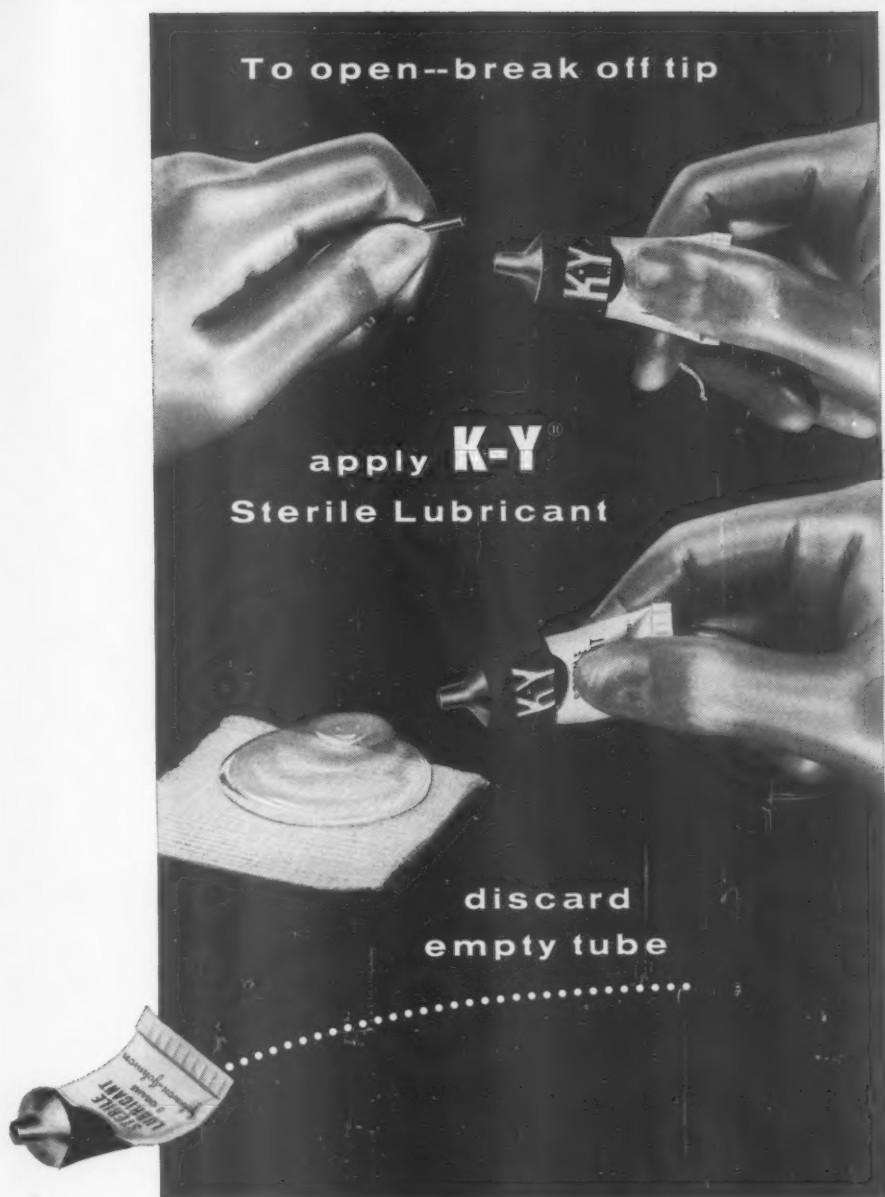
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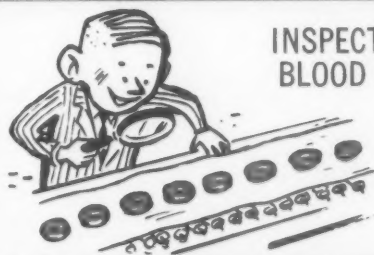
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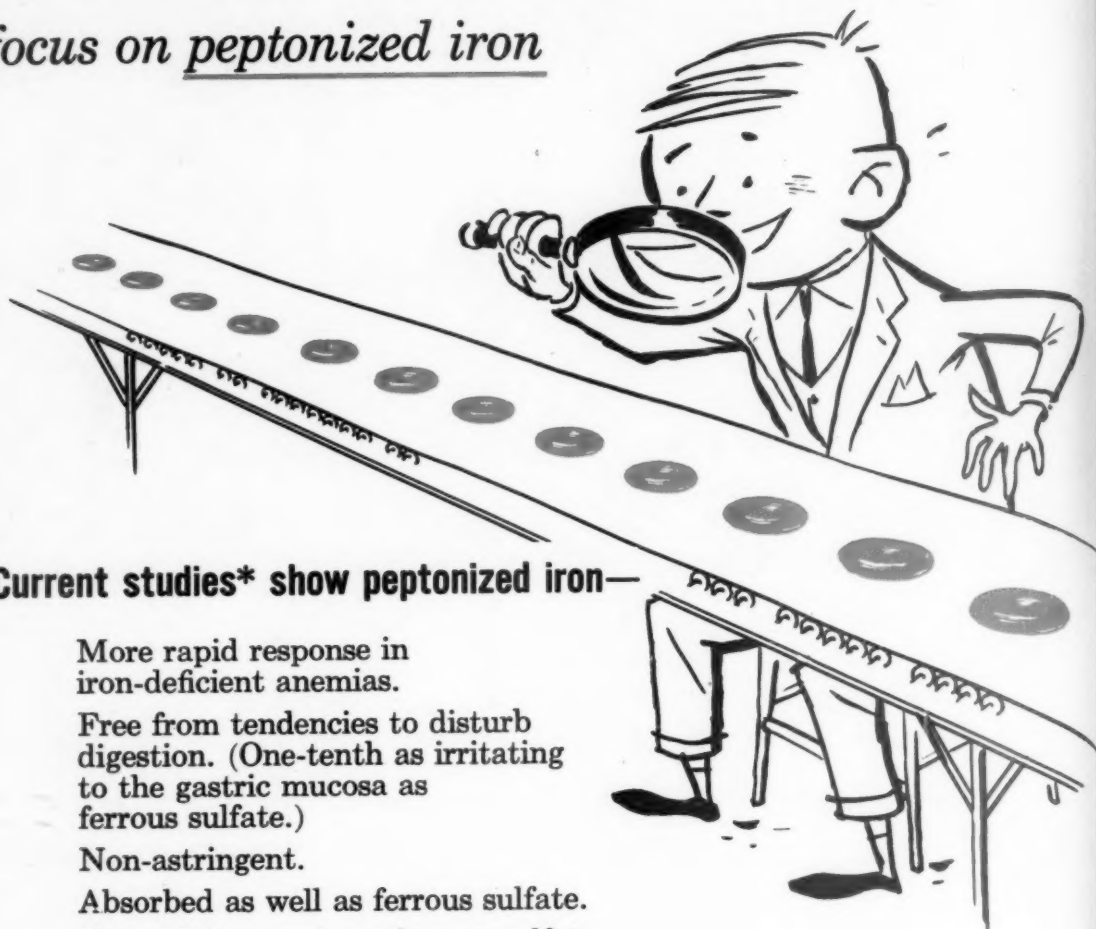
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\*Keith, J.H.: Utilization and Toxicity of Peptonized Iron  
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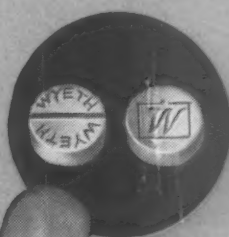
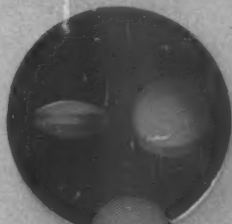
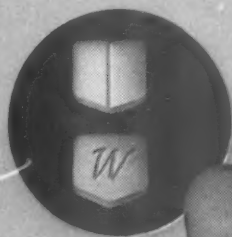
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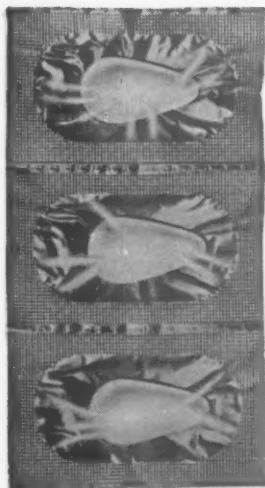


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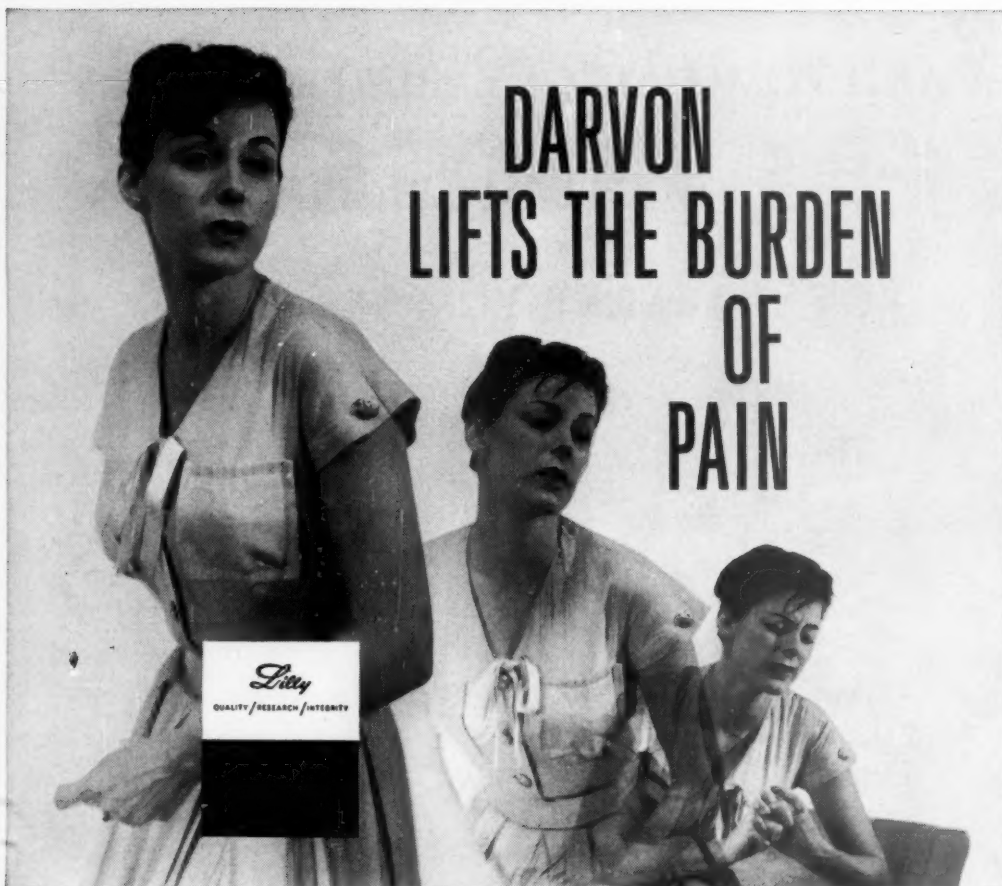
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WILLIAM J. DIECKMANN

Vol. 75, No. 1

January, 1958

*American Journal of*

OBSTETRICS AND GYNECOLOGY

*In Memoriam*

WILLIAM J. DIECKMANN

(October 20, 1897-August 15, 1957)

DR. WILLIAM J. DIECKMANN died on August 15, 1957. With his going the AMERICAN JOURNAL lost a fine editor and the specialty of Obstetrics and Gynecology one of its greatest modern leaders.

Dr. Dieckmann was born in Belleville, Illinois, on October 20, 1897, in a family where education and an intellectual life were regarded as paramount objectives. He received both his undergraduate and medical education at Washington University in St. Louis and began his professional and academic career in that institution. In 1931 he went to the University of Chicago as Associate Professor of Obstetrics and Gynecology, becoming Professor and Chairman of the Department in 1942. This post he held until 1954, when he relinquished his administrative duties in order to devote more of his time to research in his chosen subject of toxemia of pregnancy.

Membership in the local and national societies of his specialty came naturally to him and in many he served as an officer. In June, 1953, the Society of Gynecologic Investigation was founded largely through his efforts.

It was the misfortune of this writer not to know Dr. Dieckmann intimately until his later years. Yet his fame and position were clear to all in the specialty. He was known as a precise and sometimes exacting teacher, expecting of the pupil the devotion to the work that he himself was giving. He was the recognized authority in America on the toxemias of pregnancy, his textbook being the acknowledged repository of knowledge on the subject and his own work an example of painstaking search for the facts, carried on for years without the encouragement of spectacular discovery. Although he was a full-time teacher and research worker, his feeling of responsibility for the patient never faltered and his own clinical skill and knowledge were of the highest order. His insistence on the arrival at the truth by a clear and unromantic

interpretation of the currently available facts led to a certain plainness of speech that sometimes delayed friendship but eventually produced a whole-hearted confidence in his judgment and objectives.

In 1936, Dr. Dieckmann joined the staff of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, then under the editorship of the late George Kosmak, as Associate Editor. The writer of this note was appointed at the same time, but the two associate editors had little need of personal contact, for, as is well known, Dr. Kosmak was in every way "The Editor" and his associates were content with a relatively minor participation in the work and policy formation of the JOURNAL.

Upon Dr. Kosmak's retirement to the position of Honorary Editor in January, 1953, Dr. Dieckmann became one of the two "Editors" and immediately set out to reshape JOURNAL activities. The system of personal decision, which had worked so well for a generation under Dr. Kosmak, was changed, so that in many cases manuscripts were accepted or rejected only after consultation. Relations with sponsoring societies were, we believe, improved. The format of the JOURNAL, with the enthusiastic cooperation of the publishers, was modernized. Among Dr. Dieckmann's last acts was the initiation of a plan by which articles published are to some extent arranged by subject matter and so listed in the table of contents. During his short term of office, less than five years, the editorial policy of the JOURNAL was in strong and dedicated hands.

During more than the last decade, Dr. Dieckmann's life was a precarious one as a result of a cardiac condition of which he was fully aware. Although this situation is by no means uncommon in modern life, it remains an act of no small heroism to carry on, uncomplaining and unflinching, among colleagues whose lives must seem to be at least relatively secure. When death came, it was sudden, painless, and with no immediately preceding illness.

Dr. Dieckmann is survived by his wife, Katherine Morrison Dieckmann, and a daughter, Dorothy Dieckmann Brown.

There will be numerous tributes paid to William Dieckmann's memory. Many of these, especially from his professional associates in Chicago, will come with more authority because of the years of contact. Yet his brief period of service on the JOURNAL has left an indelible impression of his earnestness, his purposefulness, his devotion, and his great competency in his own field of medical practice. The short years were full and vital ones and we will not forget them.

We of the JOURNAL Staff wish then, proudly if sadly, to proclaim, "We too were his friends."

*Howard C. Taylor, Jr.*



## Obstetrics

### EFFECTIVE UTERINE BLOOD FLOW DURING LABOR

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THE fate of the fetus during pregnancy and labor is largely governed by the efficiency of placental function. This efficiency is related both to the total area of viable trophoblast across which essential metabolites reach the fetus and to the blood flow through the intervillous sinuses by which such metabolites are rendered available. Previous studies have suggested that changes in placental and myometrial circulation are closely related. We have, therefore, recently measured the effective uterine blood flow during labor since such observations might throw light on the often obscure etiology of fetal distress.

The direct measurement of blood flow in the intact human uterus during labor has offered insurmountable difficulties, but it has usually been accepted that, at the height of a contraction, the myometrial circulation must temporarily be reduced. Though we have found that the indirect clearance technique is insufficiently sensitive to measure uterine flow in the short period of a single contraction, this method used over a longer period of several contractions gives a satisfactory indication of the over-all flow in the myometrium. The present series of 48 observations were made on women during the first stage of normal or prolonged labor. Among these, three instances of fetal distress developed shortly before full cervical dilatation.

#### Method

The present series was comprised of women entered as "booked" cases in The University College Hospital of London. They were predominately primiparas with ages ranging from 19 to 35 years. Labor began normally and spontaneously in all those investigated, though in a few progress was so slow

that labor was classified as "prolonged," i.e., more than 24 hours in the first stage. Effective uterine flow measurements were made on 48 women, 20 of whom were in the early first stage and 26 in the late first stage of labor. It was also measured in 3 of these women after fetal distress became apparent.

The method of measuring effective uterine blood flow was the same that we<sup>13, 14</sup> used previously with women in the last trimester of pregnancy. It is based on the Kety<sup>8, 9</sup> tissue clearance technique which postulates that the rate of removal from a tissue of an injected diffusible ion is directly dependent upon the local circulation in that tissue.<sup>11</sup>

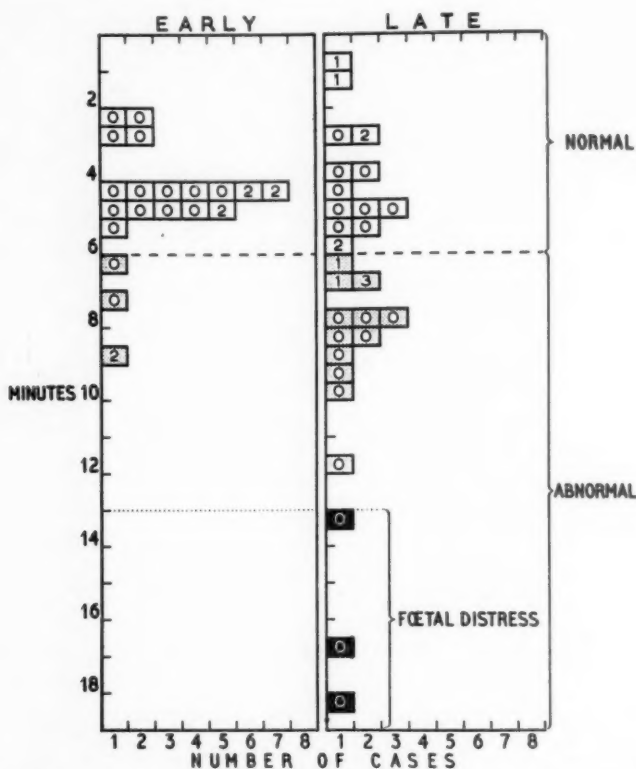


Fig. 1.—Uterine clearance times to half value for isotonic  $\text{Na}^{24}\text{Cl}$  during the early and late first stage of labor.

Figures within boxes indicate parity of the mother.

Normal clearance times

Prolonged clearance times

Prolonged clearance associated with fetal distress.

In the present study, after infiltration of the abdominal wall and parietal peritoneum with 1 per cent lignocaine hydrochloride, an injection of radioactive isotonic saline (5 to 10  $\mu\text{c}$  in 0.3 ml.  $\text{Na}^{24}\text{Cl}$ ) was made directly into the uterine muscle, the usual site being the left lower quadrant. With a little practice the needle could be felt to enter the uterine wall and at the same instant the woman often felt a deep-seated momentary pricking pain as the visceral peritoneum was pierced. This pain was trivial and was insufficient to cause anxiety in the prepared patient. To confirm that the needle was in situ, the woman was asked to take a deep rapid breath in and out; when correctly placed in the uterus the head of the needle moved sharply downward and then up as the rectus muscle contracted over the uterine muscle. Before the injection of  $\text{Na}^{24}\text{Cl}$  was made, suction was applied to the needle to make sure that it had not passed into a blood sinus or through into the liquor.



The injection was made as rapidly as possible and a screened  $\gamma$ -ray lead-cathode Geiger-Müller counter was immediately affixed with adhesive tape to the skin over the site of the injection. The removal of the initial depot in the uterine wall was noted as a function of time, counts being recorded at half-minute intervals on a counting ratemeter. Counting continued until both contraction and relaxation phases had been included. After correction for the rising background caused by release of radioactive sodium from the injection site into the general circulation, the results were expressed as "time to half value," i.e., the time taken for half the injected material to pass out from the depot. This gives a measure of the effective blood flow.<sup>19</sup>

TABLE I. UTERINE CLEARANCE TIMES FOR  $\text{Na}^{24}\text{Cl}$  IN 20 WOMEN DURING EARLY FIRST STAGE OF LABOR

CASE	PARITY	TIME TO HALF VALUE (MINUTES)	OBSERVATIONS
1	0	2.5	Entirely normal
2	0	2.5	Entirely normal
3	0	3.0	Entirely normal
4	0	3.0	Entirely normal
5	0	4.5	Entirely normal
6	ii	4.5	Entirely normal
7	ii	4.5	Entirely normal
8	0	4.5	Entirely normal
9	0	4.5	Entirely normal
10	0	4.5	Entirely normal
11	0	4.5	Entirely normal
12	ii	5.0	Entirely normal
13	0	5.0	Entirely normal
14	0	5.0	Entirely normal
15	0	5.0	Entirely normal
16	0	5.0	Entirely normal
17	0	5.5	Entirely normal
			-----Upper limit of normal
18	0	6.5	Entirely normal
19	0	7.5	Very frequent contractions
20	ii	9.0	Very frequent contractions

### Results

The results of the measurements of uterine clearance times are set out in Tables I and II and diagrammatically in Fig. 1. Table I shows the times to half value for 20 women early in the first stage of labor. In the present investigation, dilatation of the cervix to less than 3 cm. was considered as early first stage, dilatation to 3 cm. or more as late first stage. In the early first stage group, all but 3 showed normal uterine clearance times, i.e., time to half value of less than 6 minutes. Of the 3 with prolonged times, one appeared entirely normal while the other 2 had unusually frequent and strong contractions.

In the second group of 28 observations on 26 women in the late first stage of labor, 15, or more than half, had uterine clearance times longer than the normal for the quiescent uterus. Though these confinements could not be considered as "abnormal," all except one nevertheless presented features which were likely to impair blood flow in the uterine wall (see "observations," Tables I and II).

Finally, in the 3 cases in which fetal distress was present at the time of observation, the uterine clearance times were considerably prolonged and were double or more than double that regarded as the upper normal limit during

pregnancy. This finding may be interpreted as showing that the effective uterine blood flow in these cases was half or less than half that normally present, an observation which may be of considerable significance in the onset of fetal distress.

TABLE II. UTERINE CLEARANCE TIMES FOR  $\text{Na}^{24}\text{Cl}$  IN 26 WOMEN DURING LATE FIRST STAGE OF LABOR

CASE	PARITY	TIME TO HALF VALUE (MINUTES)	OBSERVATIONS
1	i	1.5	Membranes ruptured during recording
		1.0	
2	0	3.0	Entirely normal
3	0	3.0	Entirely normal
4	0	4.0	Long, quiet labor
5	0	4.0	Little meconium, fetal heart regular
6	0	4.5	Entirely normal
7	0	5.0	Entirely normal
8	0	5.0	Entirely normal
9	0	5.0	Entirely normal
10	0	5.5	Entirely normal
11	0	5.5	Long, quiet labor
12	ii	6.0	Long, quiet labor
-----			
13	i	6.5	Upper limit of normal
14	iii	7.0	Very frequent contractions
15	i	7.0	Very rapid labor
16	0	8.0	Very frequent contractions
		8.0	Long labor. Membrane ruptured 52 hours
17	0	8.0	Membranes ruptured 48 hours
18	0	8.5	Very frequent contractions
19	0	8.5	Long labor ending in forceps
20	0	9.0	Very frequent contractions
21	0	9.5	Long labor ending in forceps
22	0	10.0	Persistent cervical rim
23	0	12.0	Long, nonprogressive labor
24	0	13.5	<i>Fetal distress.</i> Long labor
25	0	17.0	<i>Fetal distress.</i> Long labor
26	0	18.5	<i>Fetal distress.</i> Long labor

### Comment

A review of the physiology of the human uterus and placenta during the last phases of pregnancy and during labor reveals considerable gaps in our knowledge. Yet it is obvious that any changes which may occur in these organs during that critical period often influence the baby's condition at birth. In recent years, however, more attention has been paid to this phase of gestation and certain features stand out more clearly. At the end of normal pregnancy there is often a progressive diminution of fetal oxygenation<sup>10</sup> which becomes more profound when pregnancy continues past term.<sup>16</sup> This change is probably in part dependent upon the alteration from fetal to adult type of hemoglobin<sup>17</sup> and must consequently be regarded as a normal progressive physiological change of a prolonged pregnancy. Though this diminution of oxygenation is usually of no danger to the fetus since there is an ample margin of safety, it may assume considerable significance in an abnormal pregnancy. At the same time that fetal oxygenation is decreased, Moore and Myerscough<sup>12</sup>

have reported that there is a progressive diminution of myometrial and, hence, placental blood flow, though here again there is usually still a wide margin of safety for the fetus. These changes, therefore, do not often endanger the child.

In abnormal pregnancy, however, complicated by pre-eclampsia, essential hypertension, twins, hydramnios, or diabetes, there may be pathological changes in the uterus and placenta which, when superimposed on those which normally occur at the end of pregnancy, greatly increase the likelihood of fetal death. Cases of severe pre-eclampsia are particularly liable to intra-uterine death. This appears to result from a combination of circumstances of which the most important is probably the diminished uterine and placental blood flow,<sup>3, 6, 7, 13, 14</sup> though in addition the amount of viable trophoblast may be reduced by infarction or inadequate placental development. Even under these adverse conditions, however, mildly pre-eclamptic pregnancies continue to term though the growth of the fetus may be impaired so that it is small and frail at birth. In an earlier study, we<sup>14</sup> showed that in both normal and pre-eclamptic women the effective uterine blood flow is diminished during exercise, a finding which in part explains the beneficial results of bed rest in pre-eclampsia and, conversely, why excessive and prolonged exercise may precipitate hypoxia in the infant.

From the foregoing brief review of the physiological and pathological changes in uterine blood flow and fetal oxygenation at or near term, it is apparent that conditions tend to be more unfavorable for the fetus at the time of birth than earlier in pregnancy and that in prolonged gestation these factors may constitute a danger in otherwise normal cases. In pre-eclampsia especially, these conditions will produce a progressively unfavorable effect.

At the onset of labor any changes in the blood flow of the uterus may be of considerable importance in relation to the survival of the child. The tension developed in skeletal muscle during a contraction has been measured by direct manometric methods<sup>2, 18</sup> as about 70 mm. Hg. Using a microballoon technique, Caldeyro-Barcia and Alvarez<sup>1, 4</sup> have shown that the tension developed in the uterine muscle at the height of a contraction is about 50 mm. Hg. During skeletal or uterine muscle contractions, the associated compression interferes with the venous return, since venous blood pressure is only in the neighborhood of 4 mm. Hg; this presumably reduces arterial blood flow by back pressure. In skeletal muscle the reduction of flow during a contraction is followed by a compensatory phase when the vessels, relaxed by the accumulation of metabolites, present an increased circulatory bed. The volume of blood flowing through a muscle over a period which includes both contraction and relaxation phases is certainly not less than that during rest. Though this aspect of hemodynamics does not appear to have been studied in the human uterus, it may be assumed that it behaves in a way similar to skeletal muscle and that a compensatory hyperemic phase follows a contraction.

If this concept of the intermittent nature of blood flow through the uterine muscle during labor is accepted, it follows that during a contraction less oxygen is transferred across the placenta. The extent of this reduction is dependent upon both the length and intensity of the uterine contraction. The ability of the fetus to withstand temporary hypoxia depends upon the degree of oxygenation between contractions. This in turn is dependent upon several factors, namely, the efficiency of the myometrial circulation, the functional integrity of the placenta, and the ability of the fetus to utilize the available oxygen. If myometrial blood flow, placental function, or the fetal circulation is impaired, the ability of the child to withstand labor will be diminished.

In the early first stage of normal labor, the infrequent and weak contractions of the uterine muscle are usually insufficient to lower oxygen tension in the fetal blood for long enough to have any adverse effect upon the baby. This is also true for the normal late first stage when the periods of rest between contractions are sufficiently long to allow the hyperemic reaction, with its increased flow, to compensate the fetus for the short hypoxia during the active phase. Indeed the findings of oxygen saturation in umbilical vessels at the time of birth<sup>5, 10, 15</sup> in normal deliveries shows that there is no gross anoxemia. In a certain number of otherwise normal labors, however, the balance between full and partial oxygenation may be upset. In the present study only women whose pregnancies had been uneventful and whose labors were expected to be normal were investigated, yet 3 in the early stage and 16 in the late first stage of labor showed uterine clearance times for  $\text{Na}^{24}\text{Cl}$  which were longer than those taken as normal before labor started.<sup>13</sup> In these 19 women the uterine flow during the first stage was the same as that previously found by us<sup>14</sup> and confirmed by Johnson and Clayton<sup>7</sup> and Moore and Myerscough<sup>12</sup> in mild cases of pre-eclampsia during the last trimester of gestation. In such pre-eclamptic women the fetus usually develops satisfactorily until term so that a uterine flow of this type must be regarded as adequate even if it may not be optimal.

In the present series no pre-eclamptic women were included, but in the light of the findings on normal women some relevant comments may be made concerning their uterine blood flow. We found that exercise decreased uterine flow in both normal and pre-eclamptic patients,<sup>14</sup> but even in the latter, where such a decrease was superimposed on an already poor myometrial circulation, there was still sufficient reserve, at least in mild cases, to maintain fetal life. A similar situation appears to occur during the majority of labors in pre-eclampsia. Although some diminution of flow must occur when contractions are frequent, in normal confinements there is a sufficiently adequate blood flow to ensure that during the hyperemic phase the fetus is sufficiently oxygenated. But in some instances even the slight reduction in oxygenation caused by the contractions of normal labor may be a source of danger when additional adverse factors, such as prolonged pregnancy or placental infarction, are present. In prolonged pregnancy, Walker and Turnbull<sup>16, 17</sup> have shown that the oxy-



gen saturation of fetal blood decreases progressively after term is passed and it is likely that in such cases even the transient reduction of myometrial flow during the contractions of labor might be a danger to the fetus. Similarly, in pre-eclampsia, where the oxygen saturation is also reduced, the diminution in blood flow may be a final factor and the child may die of asphyxia at the end of the first stage of labor.

It seems significant that, in this series, the longest uterine clearance times, i.e., 13.5, 17.0, and 18.5 minutes, were all associated with fetal distress. Distress was manifested by a failing fetal heart and meconium staining of the liquor; these had developed shortly before the uterine blood flow was measured. Formerly we had found that there was little danger to the fetus in pre-eclampsia unless the uterine clearance was much prolonged (more than 12 minutes). These findings, taken together, suggest that there may be a critical level of uterine blood flow below which the chances of intrauterine death are much increased. This hypothesis is further supported by the findings in the present study.

In the women in whom the uterine clearance was longer than normal there were generally clinical features which might be expected to reduce uterine blood flow (see "Observations," Tables I and II). Very frequent and prolonged contractions appear to be a factor of considerable importance and it is probable that the uterine tension is never properly reduced between contractions<sup>1</sup> to allow the benefit of the hyperemic phase. In labors where cervical dilatation proceeds normally, hypoxia is unlikely to jeopardize the infant's life. When there is serious incoordination of uterine activity, however, associated with frequent, powerful uterine contractions and with slow cervical dilatation, then fetal distress becomes far more probable.

In this series of normal labors there is a gradation of uterine clearance times from those which are rapid to those which must be regarded as slow. This latter group occurs in patients in whom any superimposed adverse conditions are likely to precipitate fetal distress and even intrauterine death from hypoxia.

### Summary

1. The effective uterine blood flow has been measured in 20 women during the early first stage of labor and in 26 women during the late first stage.
2. Blood flow was within normal resting limits in all but 3 instances in the early first stage, but in the late first stage 16, or more than half, showed diminished uterine blood flow.
3. Fetal distress developed in 3 cases and these all showed great reduction in the effective uterine blood flow.
4. The significance of these findings in both normal and pre-eclamptic labors is discussed. The consequent hazards to the infant are considered with reference to the etiology of fetal distress in the first stage of labor.

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## CIRCULATING EOSINOPHILS IN LABOR AND PUERPERIUM

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THE eosinophil cell of the blood has been a source of fascination to many physicians during the last fifty years. It is the only cell which is known to respond specifically to states of hypersensitivity, and it has been demonstrated that these cells are markedly attracted to the shock tissues. Kracke<sup>1</sup> affirmed that the "normal number of circulating eosinophils varies from 1-2 per cent of total white cells, or 100-200 cells cu./mm." Variations in the number of circulating eosinophils were noted as early as 1910 by Dunger.<sup>2</sup>

Pregnancy is accompanied by an increase in leukocytes and a decrease in circulating eosinophils. The stress of labor and delivery results in a rapid decrease of eosinophils. Davis and Hulit<sup>3</sup> in their significant work confirmed the finding of eosinopenia in pregnancy. This eosinopenia is supposedly due to a release of suprarenal cortical hormones of an oxysteroid nature. It is mediated through adrenal cortical stimulation by the anterior pituitary.<sup>4</sup> During pregnancy there is hypertrophy and excessive activity of the anterior pituitary and adrenal cortex. An increase in both basophilic and acidophilic cells of the anterior pituitary has been observed in pregnancy.<sup>5</sup> Circulating eosinophils are thus probably an indication of endogenous pituitary-adrenal activity.

No large study of circulating eosinophils during labor and the puerperium has been previously undertaken. Kullander<sup>6</sup> based his results on tests conducted on 15 patients in the early months of gestation, while Dawson<sup>7</sup> obtained his data from a group of 75 women. Our analysis is dependent on studies conducted on 124 pregnant women over an 8 month period in a city hospital with a fairly large obstetrical service.

### Procedure

Single testing during early labor, and 2 test examinations in the early puerperium were performed, entailing a total of 372 completed examinations. This was done according to the method of Thorn. Kullander<sup>6</sup> and Dawson<sup>7</sup> had clearly indicated that a relatively constant eosinopenia occurred from the tenth week of pregnancy onward to the day preceding delivery. Thus it was thought that a single testing obtained in the period of early labor would provide an adequate base line for the postpartum results, and would demonstrate

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the abrupt eosinopenia occurring prior to delivery. Hence, single testings were thus performed on either the first or second postpartum day, and a final sampling obtained on either the third, fourth, fifth, or sixth postpartum day. Approximately one third of the patients so tested were Puerto Ricans. The fact that these people usually have a slight eosinophilia due to parasitism was believed to have no significant influence in determining the average values achieved under various conditions.

### Results

The observation that the eosinophil level is practically constant throughout pregnancy, with the exception of the last month, has been established.<sup>6</sup>

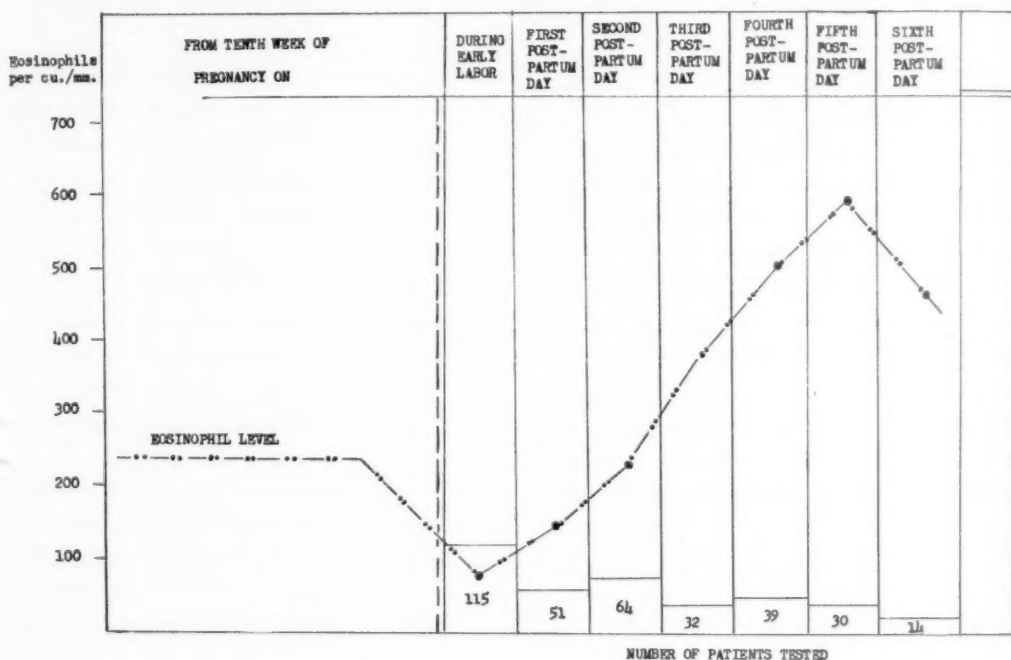


Fig. 1.—Average eosinophil levels in pregnancy and post partum.

The average is 238 to 276 eosinophils per cubic millimeter. Single testings taken during early labor demonstrated a dramatic response to the nature of stress. The eosinophil count markedly declined, and averaged 80 to 86 per cubic millimeter (Fig. 1). (The 9 cases with complications of pregnancy were not included in this study of eosinophil average count.) Fifty-one patients were tested on the first postpartum day. A poor response to the relaxation of stress was observed in 14 cases. The eosinophils either did not approach pre-delivery levels or remained stationary. Correlation of labor records showed that all of these patients had been subjected to a period of labor greater than 15 hours.

By the second postpartum day a noticeable, though in no wise striking, increase in eosinophil level was obtained. The universality of this response made correlation of labor records as regards eosinophil levels seem unprofitable, and this was not attempted.

A total of 101 eosinophil counts were performed on the third to the fifth postpartum day. Demonstrable eosinophilia was elicited, the average count

varying from 425 to 600 per cubic millimeter (Table I). This increase was noted to be in the nature of 90 per cent as compared to the pregnancy level. Patients who had an eosinophil pregnancy level bordering on high normal had postpartum increases to a proportionate level.

TABLE I. AVERAGE EOSINOPHIL LEVELS

DAY	AVERAGE PER C.MM.
Early labor	80-86
First postpartum day	130-140
Second postpartum day	220-230
Third postpartum day	380-390
Fourth postpartum day	510-520
Fifth postpartum day	590-600
Sixth postpartum day	440-450

Samplings were obtained from a small group (14 cases) on the sixth post-gestational day. Although a definite slackening was evidenced as compared to the high levels obtained during the third to the fifth day of the puerperium, the same essential facts relating to the predelivery counts held true.

Nine of the 124 patients investigated in the course of this study developed complications associated with pregnancy (Table II).

TABLE II. EOSINOPHIL VARIATIONS DURING COMPLICATIONS OF PREGNANCY

CASE	METHOD OF DELIVERY	COMPLICATION	EOSINOPHIL CU./MM. PRIOR TO DELIVERY	EOSINOPHIL CU./MM. ON 1ST P-P DAY	EOSINOPHIL CU./MM. ON 9TH P-P DAY
1. J. N. (18546-55)	Spontaneous	Thrombophlebitis	22	0	214
2. A. E. (1409-55)	Repeat C. Section	Bladder Fistula	188	0	148
3. M. W. (1737-55)	Induction of Labor outlet forceps	Pre-eclampsia	0	11	308 on 5th P-P day
4. E. B. (15454-55)	Outlet forceps	Acute Endometri- tis	22	91 4th P-P day	188 7th P-P day
5. A. G. (11175-55)	Elective C. Section	Amnionitis		42 4th P-P day	100
6. E. S. (19855-55)	Induction of Labor cutlet forceps	Placenta Abruptio Afibrinogenemia	11	0	152
7. E. S. (2111-56)	Induction of Labor outlet forceps	Eclampsia with retinal hemor- rhages	0	0	176 on 12th P-P day
8. R. E. (11227-55)	Spontaneous	Thrombophlebitis	88	99 4th P-P day	154
9. M. F. (21879-55)	Spontaneous	Breast Abscess	77	88 3rd P-P day	152

### Case Reports

Mrs. J. N., No. 185-46-55, a para iv, gravida v, was delivered on Aug. 7, 1955, of living full-term infant. On the day preceding delivery, the eosinophil level was 22 per cubic millimeter, on the first postpartum day it was 0. By the fourth postpartum day the level had increased to 94 per cubic millimeter. The patient was noted to have mild thrombophlebitis of the right leg in the region of the calf. She was placed on a regimen of antibiotics, heat cradle, and elevation of the limb, and gradual improvement ensued. By the ninth postpartum day the eosinophil level was 214 per cubic millimeter and the condition had subsided.

Mrs. E. B., No. 15454-55, para iv, gravida vi, abortion i, had an uneventful prenatal course and was delivered of normal full-term infant on July 1, 1955. The eosinophil level during early labor was 22 per cubic millimeter. The patient had a febrile postpartum course, and was treated with antibiotics. The lochia was foul smelling, and the uterus was soft, boggy, and exquisitely tender. The diagnosis of acute endometritis was entertained. The patient was treated with antibiotics, and a repeated course of ergonovine. By the fourth postpartum day the eosinophil level was 91 per cubic millimeter. On the seventh postpartum day the patient was afebrile, improved, and the eosinophil level was 188 per cubic millimeter.

Mrs. E. S., No. 2111-56, para ii, gravida iii, with an estimated date of confinement of Dec. 10, 1955, was hospitalized on Dec. 9, 1955, with signs of eclampsia, 3 plus ankle edema, 4 plus albuminuria, and blood pressure of 180/110. Proper therapy was instituted, but the patient had two convulsions and retinal hemorrhages were noted on ophthalmoscopic examination. The eosinophil level obtained at this time was 0. Induction of labor, after the symptoms subsided, was begun and the patient was delivered of a normal full-term living infant. The eosinophil level on the first postpartum day remained at 0; on the second postpartum day it was 22 per cubic millimeter. By the fifth postpartum day the level was 88. On the day of discharge (twelfth day after delivery) the eosinophil level had increased to 176 per cubic millimeter.

### Comments

It is considered that both the normal nonpregnancy eosinophil level and the level in pregnancy are controlled by the adrenal cortex, but that other factors may also operate. Venning<sup>8</sup> demonstrated that there is an initial rise in excretion of urinary corticoids in the first trimester of pregnancy which usually returns to normal by the one hundredth to the one hundred and twentieth day. The corticoids rise again to four times the normal value during the third trimester. A falling off in excretion occurs in the last month, and shortly after parturition the urinary corticoids are back to normal again. The increased adrenal-like function is most likely predominantly 11-17 oxyglucocorticoid in nature. The relative eosinophilia occurring on the third to the fifth postpartum day, when coupled with the postgestational decrease in urinary corticoids, is suggestive of an adrenocortical or adrenocorticotrophic hormone withdrawal syndrome.

The pattern of circulating eosinophils is similar to that described by Gabrilove<sup>9</sup> following operative procedures. There is a sharp rise in eosinophils about the third to the fifth day post delivery; this is in direct proportion to the pregnancy level, being higher in those with higher pregnancy counts.

Continued eosinopenia, first noted by an abrupt descent occurring before delivery and sustained for a variable period during the puerperium, is indicative of complications associated with the pregnant state. Schilling<sup>10</sup> described an eosinopenia in the course of acute infections and regarded the failure of the eosinophils to return to the circulating blood as a grave sign. Our cases of mild thrombophlebitis and endometritis may be so categorized (Table II).

Eclampsia is a complication of pregnancy that may have its origin in abnormal steroid metabolism. The absolute eosinopenia which is encountered during the convulsive seizures (Table II) may represent sudden stress and compensatory adrenal cortical activity, perhaps mediated through the pituitary gland.



Surgical intervention represents trauma, and the eosinopenia is the natural adrenal cortical response (Selye's "alarm reaction"). Labor produces a period of physiologic stress which is easily combated by normal adrenal functions. It is possible that some of the previously unexplained states of shock in pregnancy and labor may well have their origin in transient pituitary or adrenal cortical failure.

### Summary

1. The normal number of circulating eosinophils varies from 100 to 200 cells per cubic millimeter. Eosinopenia occurs early in pregnancy (the tenth week); an abrupt decrease is noticeable on the day preceding delivery (early labor).

2. A very sharp decline in eosinophils to zero levels during early labor or a poor response on the first postpartum day may be suggestive of a long and difficult delivery.

3. Overaction of the hypophyseal adrenocortical endocrine complex results in a decrease of eosinophils. This relative eosinopenia is statistically significant. These changes probably represent increased adrenocortical activity, long continued during pregnancy, reaching a climax in parturition.

4. One hundred and twenty-four patients were investigated and 372 individual tests conducted. Nine patients had complications associated with the pregnant state.

5. A rise in circulating eosinophils occurs on the third to the fifth postpartum day. This increase is in the realm of 90 per cent as compared to pregnancy levels.

6. The lessened rise or even fall of eosinophils in the cases with postpartum complications, as compared to the characteristic rise in uncomplicated cases, is attributed to the stresser characteristics of the complications and their relative severity. The poor response to the stress withdrawal syndrome is indicative of an underlying pathological state occurring in the puerperium.

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## EFFECTS OF ANESTHETIC AND SEDATIVE AGENTS COMMONLY EMPLOYED IN OBSTETRIC PRACTICE ON ISOLATED HUMAN UTERINE MUSCLE

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IMPRESSED with the variety of anesthetic, analgesic, and sedative drugs employed in obstetric practice and the paucity of data concerning the effects of such agents upon human uterine function, a program of research was undertaken in the hope of increasing our knowledge in this respect. Since no practicable method exists for obtaining the information desired from the human uterus in situ<sup>1</sup> and earlier research<sup>2</sup> has shown electromyographic studies to be inapplicable—i.e., uterine bioelectric activity continued essentially unaltered following prolonged anoxia or exposure to high concentrations of ether—it was considered desirable to employ mechanograms of human uterine muscle in vitro as a means of assay. This approach was selected, moreover, because bioelectric changes are not invariably representative of the degree of smooth muscle tension developed during contraction nor, indeed, present in the quiescent state (tonus).

### Methods

Muscle strips of 1.2 to 1.8 grams in weight were obtained from 42 gravid and nongravid uteri, either at cesarean section or following hysterectomy. These strips were suspended in oxygenated Locke's solution at 37° C. and so arranged as to actuate an ink-writing lever held by gravity against a slowly moving (2.2 cm. per minute) kymograph drum. This arrangement served to minimize friction in the recording system. Although but a few (5 to 15) minutes elapsed between excision of the tissues in the operating room and the suspension of the muscle strips in the Locke's solution, frequently little or no spontaneous activity was apparent for rather extended periods of time. This was particularly noticeable in sections from the gravid organ and in tissues excised from the uteri of postmenopausal women, when contractions occasionally failed to appear for as long as 2 to 3 hours after the tissues were placed in the bath.

After a satisfactory control record had been secured, the tissues were exposed to the various agents selected for study. In observations on the effects of the volatile anesthetics it was found impossible to assess dosage accurately.

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This was because the direct addition of a measured amount of ether, for example, resulted in the speedy reduction of the drug's concentration by evaporation due to the temperature of the bath coupled with the agitation essential to adequate oxygenation. For this reason the inhalation anesthetics were administered in the form of vapors, with oxygen, for varying periods of time. All

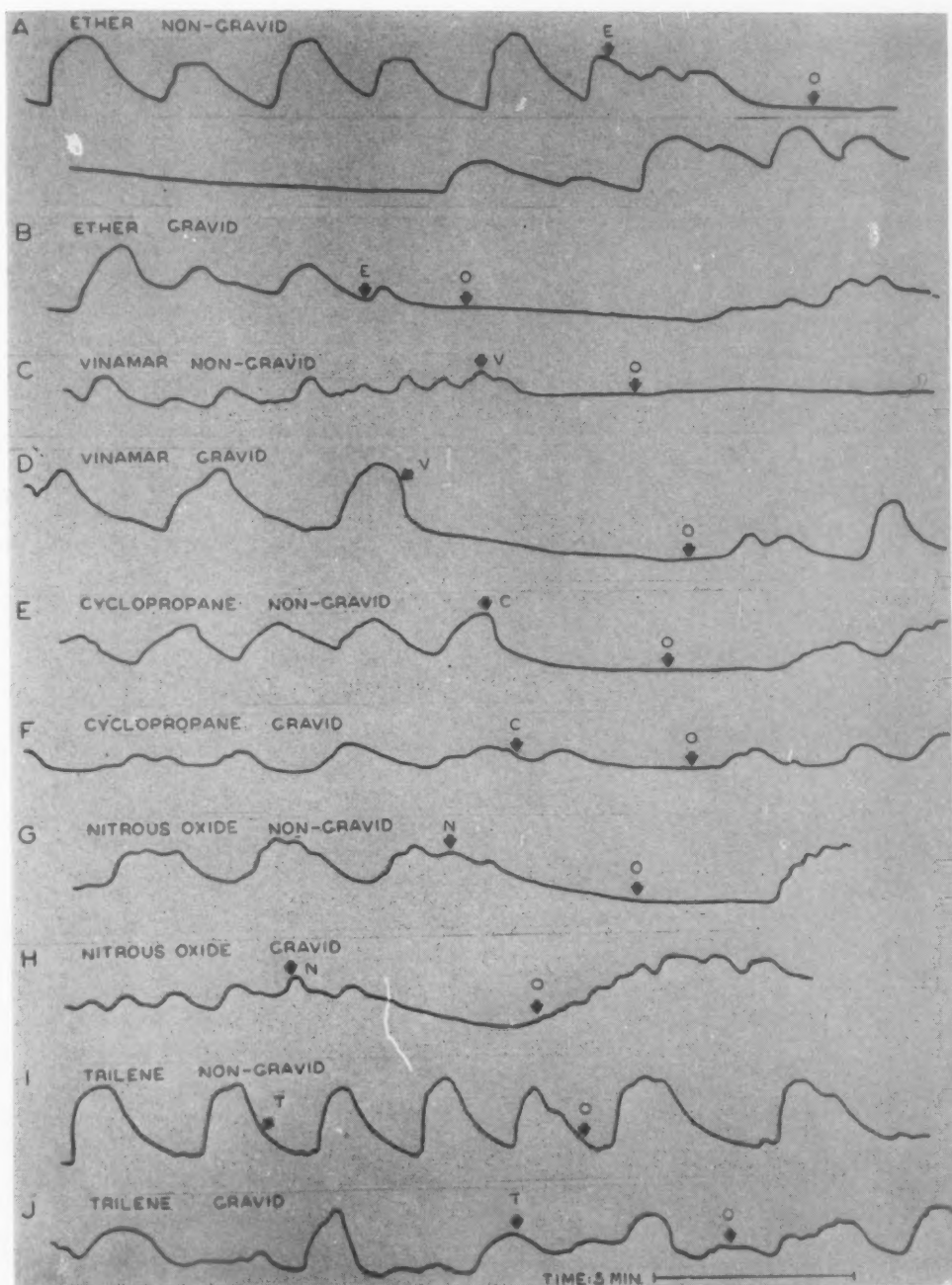


Fig. 1.—Effects of volatile anesthetics on the mobility of muscle strips excised from nongravid and gravid human uteri. These agents were admitted to the tissue chamber in the form of vapors, in conjunction with oxygen, as indicated by arrows. Anesthesia was halted in each case at O, and oxygen vapor, alone, bubbled through the Locke's solution.

other agents were added to the Locke's solution within the muscle chamber on the basis of their calculated concentrations following the customary clinical dosage and equilibration within an assumed extracellular space of 10,000 ml. for a woman of average body weight. This initial dosage was subsequently increased to 5, and later to 10 times such concentration. This dosage schedule

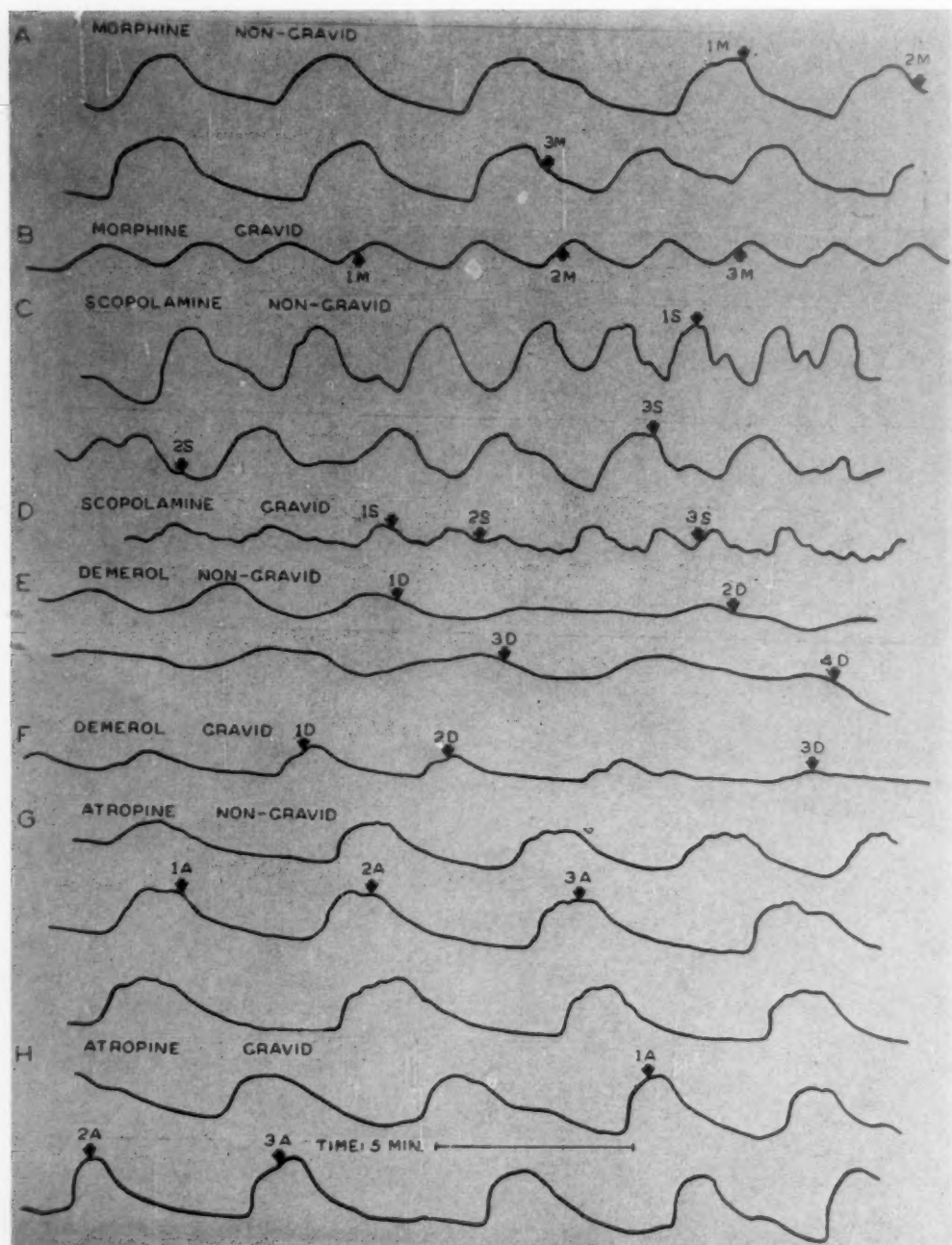


Fig. 2.—Effects of various preoperative medicaments on human uterine motility. Following control runs, each drug was added to the muscle chamber as indicated by the numerals 1, 2, 3, and 4. At 1, the concentration of each drug approximated that estimated to be present in the extracellular space following the administration of the usual clinical dosage to a patient if the volume of equilibrium distribution of the drug were limited to the extracellular water. Numerals 2, 3, and 4 indicate 5, 10, and 20 times such concentration.



was adopted in an attempt to mimic the effect of such drugs when they are (a) at minimum concentration (as if at equilibrium distribution within the patient); (b) confined to the blood stream; and finally (c) at highest concentration during the first circulation following intravenous injection.

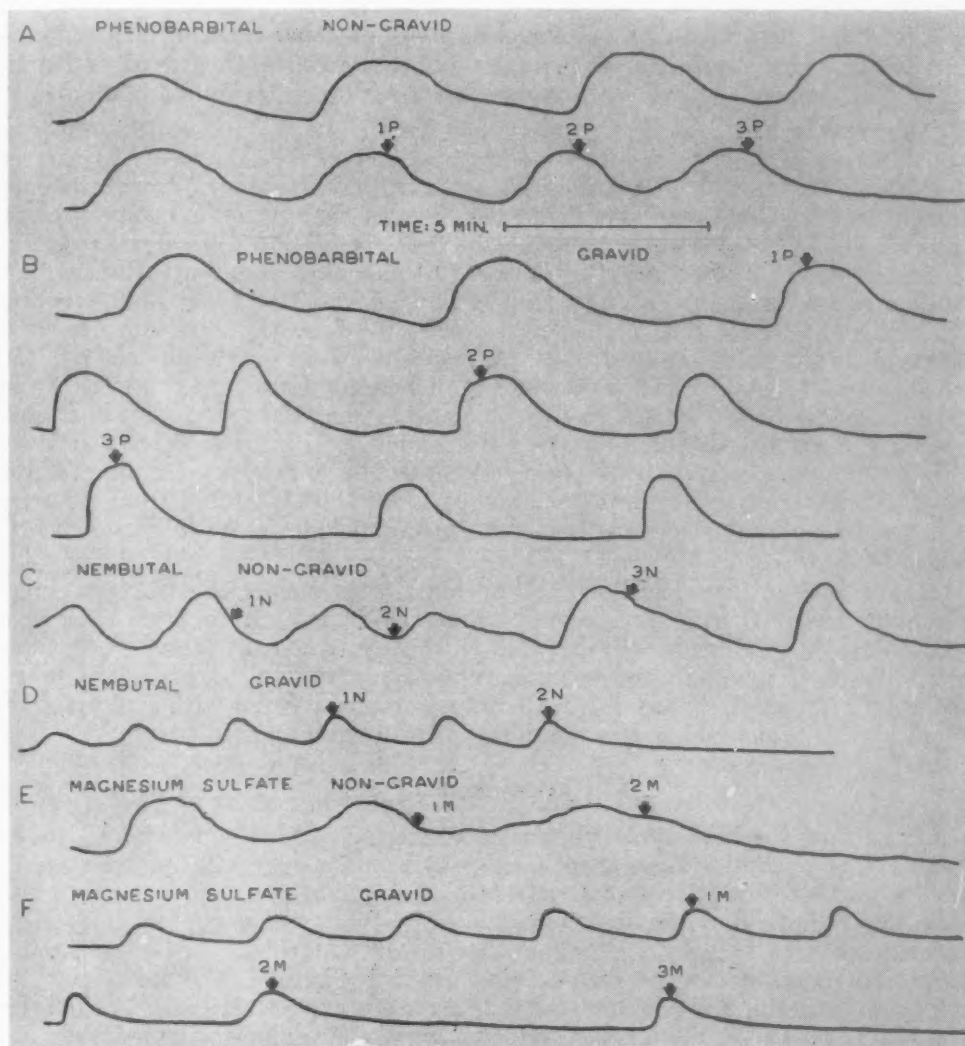


Fig. 3.—Further experiments with commonly employed sedative agents. The numerals 1, 2, and 3 indicate concentrations of the drugs as in Fig. 2.

During all control periods no significant difference appeared in the rate of contraction of muscle strips taken from gravid, as compared with non-gravid uteri. This rate averaged 0.28 and 0.27 per minute in samples taken from 25 gravid and 17 nongravid uteri, respectively.

### Results

In 18 tests on tissues from 7 nongravid and 8 gravid uteri, exposure to oxygen-ether vapor resulted in an almost immediate cessation of uterine motility with marked loss of tone as illustrated in Fig. 1, A and B. Recovery was protracted, averaging 5.9 minutes of intense oxygenation before a return of contractility became evident.



Vinyl ether (Vinamar\*) (Fig. 1, *C* and *D*) was found to be equally inhibitory to uterine muscle activity in 17 trials, and decreased tonus persisted even after an apparent recovery of normal contractility had taken place. Similar results followed the administration of both cyclopropane vapor and nitrous oxide gas (Fig. 1, *E*, *F*, *G*, and *H*). Trichloroethylene ("Trilene") vapor, on the other hand, had little or no observable effect on either contractility or tonus in 12 trials when administered to tissue samples from both gravid and non-gravid uteri in conjunction with oxygen for an average period of 4 minutes.

As shown in Fig. 2, *A*, *B*, *C*, and *D*, morphine (9 trials) and scopolamine (12 trials) had no demonstrable effect on uterine activity. In the case of Demerol (11 trials) no alteration in uterine muscle motility was observed until the concentration of the drug had been increased to twice that estimated to be present in the blood stream of a patient during the first circulation following the intravenous injection of 100 mg. of the drug. At such high concentration, a definite decrease in muscle tonus occurred (Fig. 2, *E* and *F*). The administration of atropine (Fig. 2, *G* and *H*) had no significant effect on tissue samples from non-gravid or gravid uteri in any of the concentrations employed in 11 trials. Phenobarbital (Fig. 3, *A* and *B*) did not influence the pattern of contractility in any of the concentrations used in 4 experiments. Nembutal had no demonstrable effect on the activity of tissue samples from non-gravid uteri in 6 tests (Fig. 3, *C*), but depressed activity was observed following exposure of muscle strips from 3 gravid uteri to a concentration equivalent to that estimated to be present in the extracellular space of a woman receiving a total of 7.5 grains of this drug (Fig. 3, *D*).

Magnesium sulfate decreased the periodicity of spontaneous uterine muscle contraction in 8 preparations from non-gravid and gravid uteri with progressive loss of tone in doses estimated as the equivalent of 2 Gm. of the salt limited in distribution to the vascular compartment in a patient of average body weight (Fig. 3, *E* and *F*). All tissue samples treated with this drug exhibited loss of tonus which was maximal in those from gravid uteri.

### Comment

Ether, vinyl ether, cyclopropane, and nitrous oxide were found to be depressant to excised muscle from both gravid and non-gravid human uteri in vitro. Due to technical reasons cited, the concentration of these anesthetics in the tissue bath may not be comparable to that necessary for obstetrical anesthesia in vivo. However, numerous clinical studies<sup>3-7</sup> attest their inhibitory action on the gravid uterus, it being generally agreed that the deeper the level of anesthesia, the greater the degree of uterine relaxation. Further, since the activity of the excised uterine strips diminished immediately on administration of the above anesthetics and returned on dissipation of these agents from the muscle bath, it is felt that a direct inhibition of the contractile fibers of the uterus is involved.

Trichloroethylene has been said to decrease uterine tone after prolonged administration in vivo.<sup>8, 9</sup> However, no depression of tone or force of contraction was observed in muscle strips from gravid or non-gravid uteri in vitro, suggesting that any inhibitory action of this drug must be central in origin.

The action of morphine sulfate on the contractility of the uterus has been studied extensively, and Bickers<sup>10</sup> has concluded that small doses lower uterine tonus and prolong the intervals between contractions. Rucker,<sup>11</sup> however, found no depressant action unless morphine dosage was in excess of 10 mg.

\*Vinamar, manufactured by Ohio Chemical and Surgical Equipment Co., Madison, Wis.

Dodek,<sup>12</sup> employing an external hysterographic method in women at term, concluded that morphine did not impede labor, and this observation was confirmed by Caldeyro-Barcia,<sup>13</sup> who used intrauterine balloons to record the amniotic fluid pressure. In the present study, morphine sulfate was without effect on muscle samples from gravid and nongravid uteri even at concentrations estimated to be present in an aliquot of blood during the first circulation following injection, indicating that any depressant action of morphine on the uterus must be central rather than peripheral in origin—a condition demonstrated to be true in the dog and rabbit.<sup>14</sup>

Demerol (meperidine) had no effect on human uterine tissue in vitro in a dosage equivalent to that usually administered in clinical practice. Higher dosages resulted in a decrease in muscle tone and frequency of contraction, indicating that the reported shortening of labor attributed to this medicament<sup>15</sup> cannot be due to a direct stimulation of the uterine musculature.

The postganglionic, cholinergic blocking agents (atropine and scopolamine) were without effect on either tonus or contractility of muscle tissues isolated from gravid and nongravid uteri, a finding which we have interpreted as indicating the absence of any direct action of these agents upon the uterine myometrium. Phenobarbital, in like manner, exerted no demonstrable effect on any of the muscle strips tested in any of the dosages employed, while Nembutal was inhibitory with increased dosage.

Uterine muscle from both gravid and nongravid uteri exhibited loss of force and frequency of contraction in the presence of magnesium sulfate within the tissue chamber. This observation was interpreted as representing the spasmolytic action of the magnesium ion as described by Abarbanel<sup>16</sup> and extends his findings to include the nongravid organ. It further demonstrates that at least a part of this spasmolytic action is a direct effect of the ion on the contractile fibers of the myometrium.

### Summary

1. An attempt to assay the effects of commonly employed anesthetic and sedative agents on human uterine muscle tissues is described.
2. All of the inhalation anesthetics tested were found to be markedly depressant to gravid and nongravid uterine muscle activity in vitro, with the single exception of trichloroethylene.
3. Morphine, scopolamine, Demerol, atropine, and phenobarbital produced no significant effect on the activity and tonus of uterine muscle samples obtained from both nongravid and gravid uteri.
4. Nembutal was found to be without marked effect on tissues from nongravid uteri, but to possess a depressant action on samples from the gravid uterus when in sufficiently high concentration.
5. Magnesium sulfate depressed contractility and lowered tonus in muscle strips from both nongravid and gravid uteri.

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## AN EVALUATION OF THE ACTION OF RELAXIN ON ISOLATED HUMAN UTERINE MUSCLE AND CERVICAL TISSUES IN VITRO

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IN 1812, Le Gallois<sup>1</sup> described relaxation of the pelvic ligaments of the guinea pig associated with pregnancy. This observation has been recorded in many mammalian species including the primates.<sup>1-10</sup> Hisaw<sup>11-13</sup> first demonstrated that relaxation of the pelvic ligaments is attributable to a hormone which he termed "relaxin," elaborated by the ovary, placenta, and uterus. Recent studies<sup>14, 15</sup> have shown that this hormone has the additional property, in the guinea pig and rat, of inhibiting uterine contractility. Several clinical reports<sup>16-18</sup> describe attempts to evaluate this inhibitory action of relaxin during premature labor in women.

A recent study in this laboratory<sup>19</sup> has shown that certain agents (ether, cyclopropane, etc.) are capable of inhibiting the spontaneous contractions of human uterine muscle strips suspended in a tissue bath. These observations suggested the practicability of quantitatively assaying the action of relaxin\* on human uterine muscle and cervical tissues in vitro.

### Methods

Tissue strips from the fundus and cervix of 8 gravid and 7 nongravid human uteri were obtained at cesarean section or hysterectomy and suspended in oxygenated Locke's solution at 37° C. Kymographic recordings of the spontaneous activity of the tissues were obtained by means of a light ink-writing lever held in contact with a rotating drum by gravity alone. After a suitable control period, relaxin was added to the tissue chamber in concentrations of 1/2,000, 1/500, 1, 5, and 10 times that calculated to be present in an extracellular space of 10,000 ml. in a patient treated with 60,000 guinea pig units of the hormone.

### Results

Fig. 1 depicts the effect of relaxin on the activity of nongravid human uterine muscle. The arrows indicate the experimental procedures, and dosage is expressed in gammas per milliliter of Locke's solution within the tissue chamber. In Fig. 1, A a characteristic mechanogram is recorded prior and subsequent to the administration of relaxin without demonstrable inhibitory effect. Since it was considered that tissue samples demonstrating this high

\*The preparation used in this study was supplied by the Warner-Chilcott Laboratories in the form of Releasin, through the kindness of Dr. Robert Kroc.

degree of contractility might not be responsive to relaxin, a muscle strip contracting with less intensity was employed, as shown in Fig. 1, *B*. The hormone produced no discernible effect. Ether vapor was admitted to the tissue bath in order to demonstrate that the motility and tone of the strip could be depressed, as in an earlier study.<sup>19</sup> With the cessation of exposure to ether, contractility was restored despite the presence of a relaxin concentration calculated as the equivalent of 600,000 guinea pig units administered to a patient with an extracellular space of 10,000 ml.

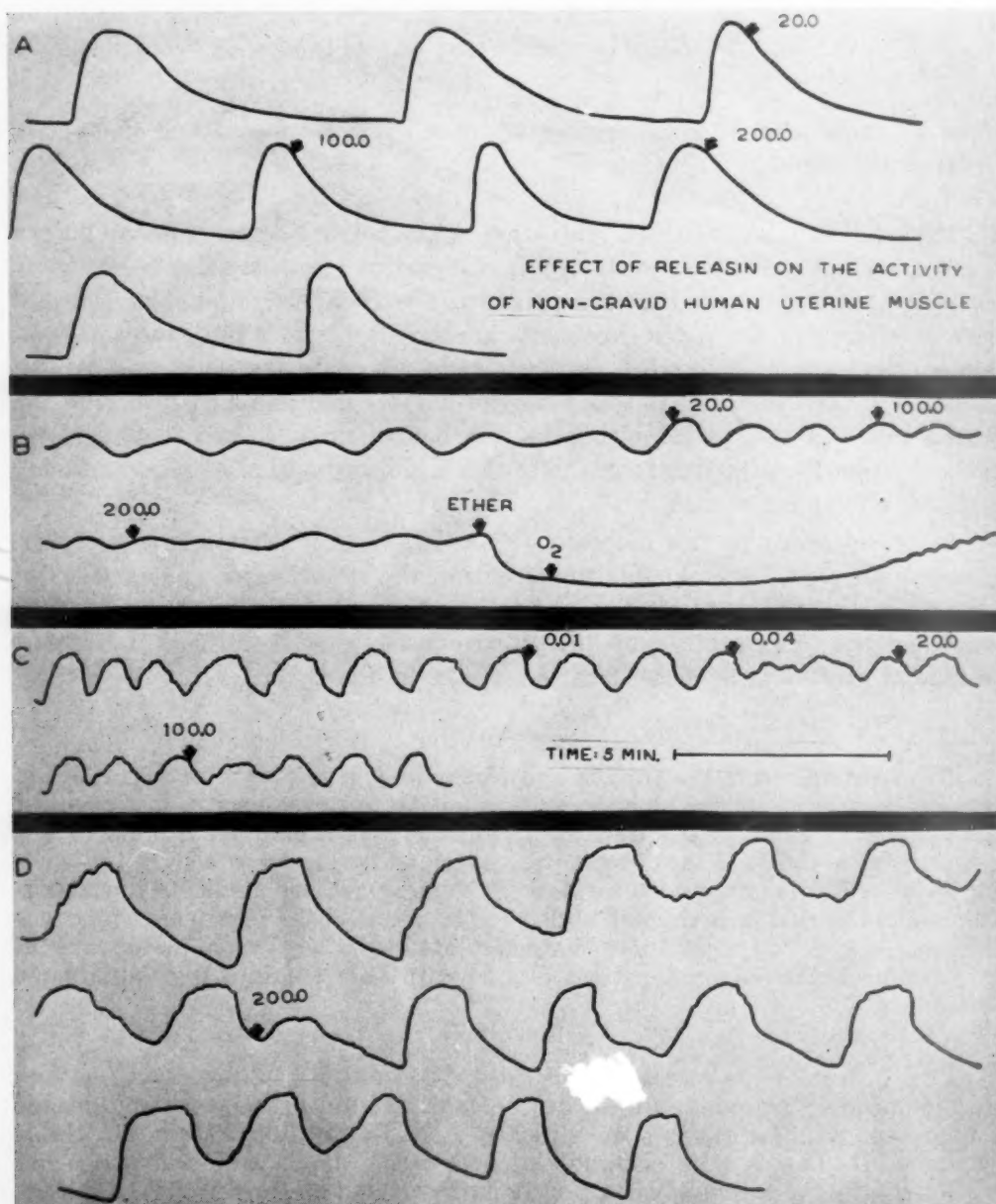


Fig. 1.—Effect of relaxin on the contractility and tonus of nongravid human uterine muscle. Arrows indicate the experimental procedures throughout and dosages are expressed as gammas of the hormone per milliliter of Locke's solution in the muscle chamber.



In order to eliminate the possibility of excessive dosage, reduced amounts of the hormone were used, as shown in Fig. 1, *C*. Again, no inhibitory effect of the drug was observed. The possibility of the occurrence of tachyphylaxis, due to the use of multiple exposures to the drug, was considered, and in an additional experiment (Fig. 1, *D*) the tissue was treated with a single, massive dose without effect. This record also shows the continued, spontaneous alterations in tone so characteristic of smooth muscle.

Fig. 2 represents experiments in which relaxin was assayed on near-term, gravid uterine muscle obtained from the mid-portion of the anterior uterine wall at cesarean section. Fig. 2, *A*, shows that relaxin exerted no inhibitory effect on uterine activity, but ether vapor quickly stopped contractions and

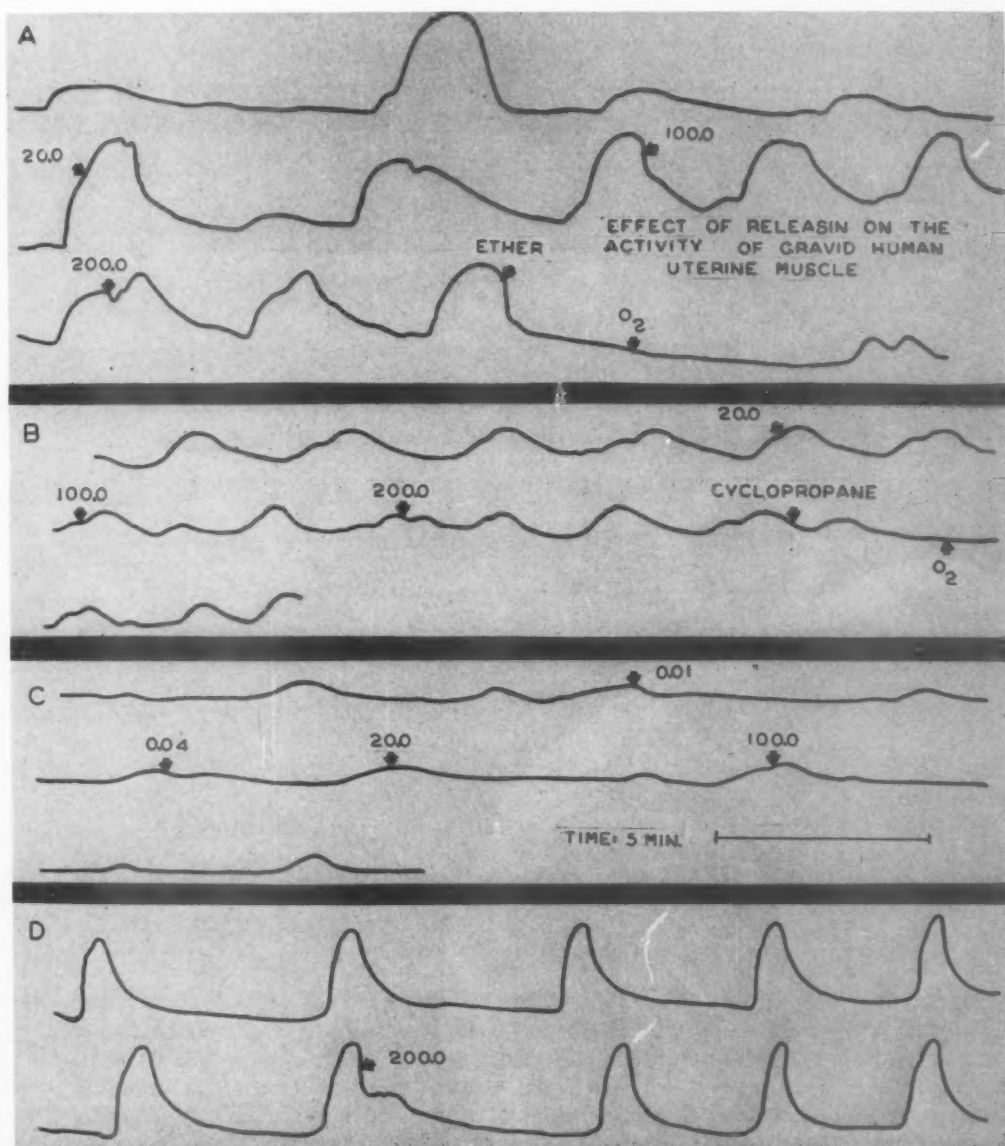


Fig. 2.—Effect of relaxin on the contractility and tonus of gravid human uterine muscle. Procedures and dosages are as indicated in Fig. 1.

reduced tone. Furthermore, after ether administration was discontinued, contractility and tone returned despite the presence within the bath of a high concentration of relaxin. Fig. 2, *B* was recorded from a weakly contracting strip of gravid uterine muscle, tested in order to demonstrate that a high order of

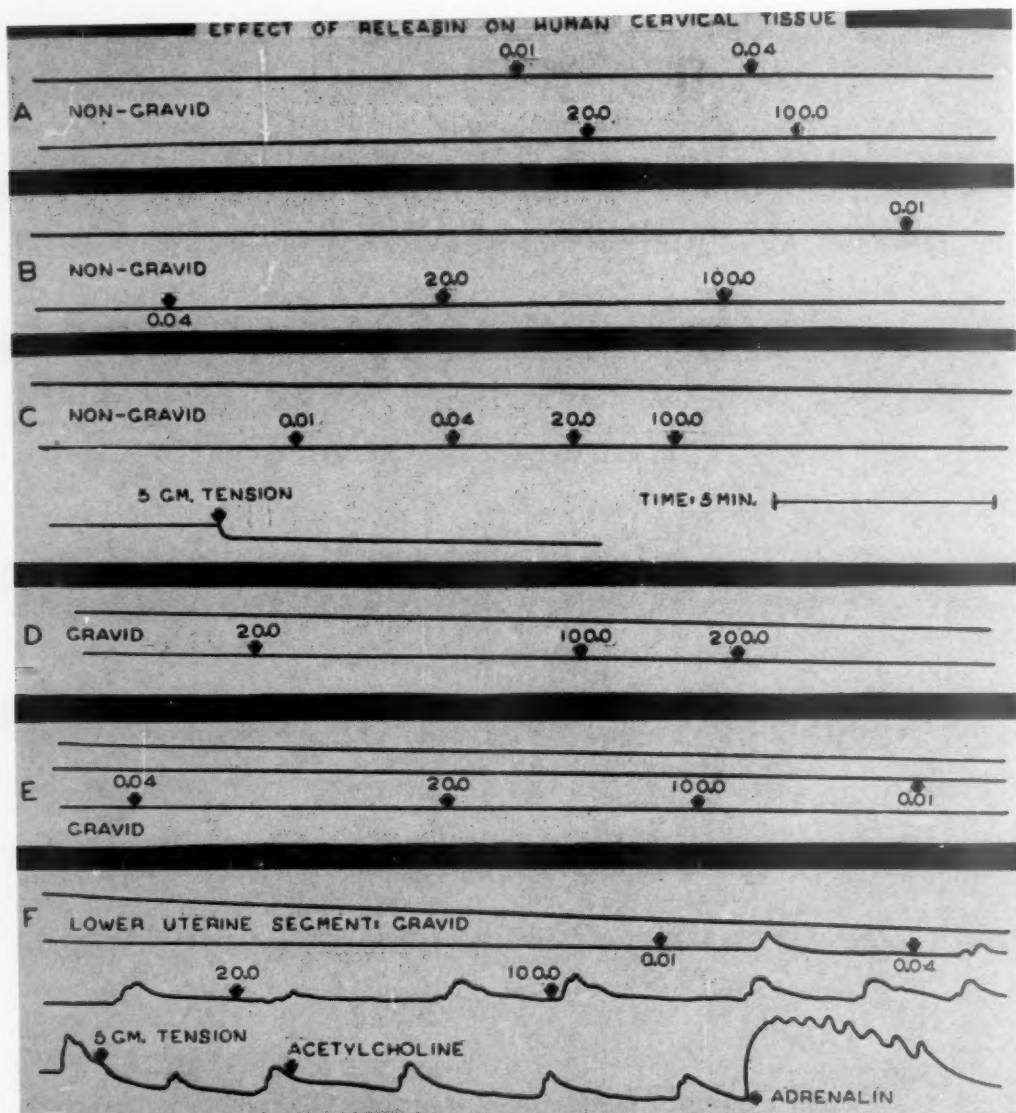


Fig. 3.—Effect of relaxin on cervical tissue excised from nongravid and gravid human uteri. Procedures and dosages are as indicated in Fig. 1.

contractility was not masking a possible relaxing effect of the drug. In addition, cyclopropane vapor was bubbled through the bath with complete inhibition of contraction during its administration. In Fig. 2, *C* a weakly contracting muscle strip was studied, with the employment of the small dosages previously used in tests of uterine muscle from nongravid uteri. All exposures to the hormone were without appreciable effect. Record 2, *D* illustrates the lack of discernible effect of a single exposure to a high concentration of the hormone, eliminating tachyphylaxis as a factor responsible for the negativity of results in the gravid series.

Records obtained from strips of cervical tissues are shown in Fig. 3. Tracings 3, A and B are from 2 typical experiments in which relaxin produced no visible decrease in tension in cervical tissues from that of non gravid uteri. Fig. 3, C is another demonstration of the lack of response to the hormone in such tissues, to which an additional 5 grams of tension was added to make certain of the sample's capability for further lengthening. Fig. 3, D and E show the absence of any demonstrable relaxation in cervical tissues obtained from gravid uteri.

The experiment illustrated in Fig. 3, F proved most interesting. The tissue was obtained from the caudad side of a transverse incision into the lower uterine segment at cesarean section in the same manner as were the other gravid cervical samples. This strip, however, contained at least some contractile fibers, for shortly after the administration of the first test dose of relaxin, contractions were observed. It is not contended that this activity was precipitated by the hormone, but rather that its occurrence at this time was fortuitous. However, the onset of spontaneous contractions immediately following the administration of relaxin is rather strongly indicative of its benign effect on human uterine tissue. Five grams of weight was added as indicated on the record and gave evidence of the capacity of the strip for further lengthening. Later acetylcholine (1:50,000) was added to the tissue bath without effect, while Adrenalin (1:100,000) resulted in immediate and sustained contraction. This reaction to acetylcholine and Adrenalin is typical of gravid uterine tissue in our experience, and appeared to be unaltered by the presence of relaxin.

### Summary

1. Relaxin had no demonstrable effect on the spontaneous contractility of isolated human uterine muscle, or on the tension of cervical tissues in vitro.
2. This was true for tissue samples taken from both non gravid and gravid uteri.
3. It appears that the evaluation of relaxin as an adjunct to the armamentarium of the obstetrician and gynecologist must await the result of extensive clinical experience and trial.

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## ELECTIVE INDUCTION OF LABOR

### Analysis of 500 Cases

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THE use of Pituitrin (hypophamine) for elective induction of labor has long been a controversial issue. From the early twenties to the late forties, this practice was largely condemned. Then in 1947 Eastman<sup>1</sup> showed that Pituitrin could be used in labor without serious complications, and in the same year Grier<sup>2</sup> reported a series of 129 patients in whom labor was induced electively by small intramuscular doses of Pitocin (alpha-hypophamine) with a gross fetal mortality of less than 2 per cent. Following these reports a change in attitude toward the use of this drug in obstetrics swept the entire country, and the indications were increased perhaps with more enthusiasm than discrimination.

In the past 5 years, discussions, both pro and con, on the use of Pitocin in labor, especially in elective induction done for reasons other than medical or obstetric, have flooded the literature. There is an abundance of well-documented reports<sup>3, 4, 5</sup> on elective induction coming from well-known institutions claiming the safety of this procedure for both mother and child. On the other hand, probably an equal or even greater number of clinics and obstetricians take a more cautious attitude, supported by equally authentic figures. This latter group claims that, in the hands of the inexperienced, Pitocin is a very dangerous drug, one that can give rise to serious complications for both mother and baby. Because of the popularity of this procedure, they say, it can be very easily abused and misused. They also point out that the legal status of elective induction of labor has not as yet been defined.

A recent survey by Hellman and his associates<sup>6</sup> of statistics taken for The Obstetrical Statistical Cooperative, chiefly by university institutions, shows how widely the attitudes of these institutions vary on the use of Pitocin in labor, especially for elective induction. Thus it may be concluded that at present the status of purely elective induction of labor is still a highly debatable issue. Its incidence, however, has increased considerably in the past few years. We therefore believed an evaluation of results in this hospital, which has one of the largest private obstetric services in the state, was imperative, and in 1956 we began a study of all cases of purely elective induction of labor.

#### Material and Methods

From Jan. 1, 1956, to Feb. 28, 1957, we studied 500 consecutive cases of elective induction at the Millard Fillmore Hospital done for reasons other than



medical or obstetric. Patients who were admitted with ruptured membranes were excluded. In this 14 month period, there were 5,638 deliveries; thus the incidence of purely elective induction was 11.07 per cent, and 52 per cent of the cases were from the services of 3 obstetricians.

There were 100 primiparas in the series and 400 multiparas, 93 per cent of whom had a parity of from two to four. The youngest primipara was 17 and the oldest 39 years old; the youngest multipara was 19 and the oldest 43 years. All patients were within 2 weeks of the expected date of confinement.

We should like to emphasize that we have no control over the selection of patients for induction, as they are all private patients of Board qualified and certified obstetricians. It is to be expected, therefore, that there will be some variation in the individual obstetrician's criteria for a "ripe" cervix, favorable for induction. In order to establish uniformity in the interpretation of the cervical findings, we examined these patients before induction was started (one of us examined nearly all of them), noting particularly the consistency of the cervix, dilatation, effacement, and station of the presenting part. These patients were then followed through their labor, delivery, and puerperium, up to the time of discharge from the hospital. Follow-up on the babies was limited to this extent, except for one baby whose follow-up was extended to a few days over one month.

TABLE I. GESTATION, PRESENTATION, AND METHOD OF INDUCTION, 500 CASES

	PRIMIPARAS (100 CASES)		MULTIPARAS (400 CASES)	
	NO. OF CASES	% OF TOTAL CASES	NO. OF CASES	% OF TOTAL CASES
<i>Gestation (weeks).—</i>				
38-39	25	25	115	26.25
40	51	51	228	57.0
41-42	24	24	57	16.75
<i>Presentation.—</i>				
Vertex	100	100	396*	99.0
Breech	0	0	6*	1.0
<i>Method of Induction.—</i>				
Intravenous	26	26	83	20.75
Intramuscular	63	63	300	75.0
Combined intravenous and intra-muscular	10	10	14	3.5
Rupture of membranes	1	1	3	0.75

\*Includes 1 set of twins.

The methods of induction in both groups were of four types: (1) intravenous infusion of Pitocin (1 ampule of Pitocin, containing 10 I.U. per milliliter, in 1,000 c.c. of 10 per cent dextrose in water, given at a rate of 10 to 30 drops per minute); (2) intramuscular injection of small doses of Pitocin (1 ampule or 10 I.U. per milliliter of Pitocin diluted with 10 c.c. of calcium-gluconate-quinine solution, given fractionally at intervals of 30 to 60 minutes or more, depending on the progress of labor); (3) combined intramuscular and intravenous Pitocin, same dose, given when the first method failed to elicit a satisfactory response (in all 3 methods artificial rupture of the membranes either followed or preceded the administration of Pitocin); (4) artificial rupture of the membranes alone.

Intramuscular injection of Pitocin was the procedure of choice in 72 per cent of the cases, being the most practical here, although there has been a definite increase in the use of the intravenous method. For a proper evaluation of our results, however, it should be noted that the latter method was employed in some cases in which the "ripeness" of the cervix was less than ideal.



TABLE II. COMPARISON OF LATENT PERIOD IN FAVORABLE AND UNFAVORABLE CASES (PRIMIPARAS)

METHOD OF INDUCTION	LATENT PERIOD												FAILED INDUCTION		TOTAL CASES	
	30 MINUTES OR LESS		31 TO 60 MINUTES		61 TO 90 MINUTES		91 TO 120 MINUTES		121 TO 240 MINUTES		241 TO 480 MINUTES		OVER 8 HOURS			
	F*	U*	F	U	F	U	F	U	F	U	F	U	F	U		
Intravenous	12	1	4	2	-	-	2	-	-	2	-	-	3	18	8	
Intramuscular	18	-	23	3	6	3	1	-	5	1	-	-	3	53	10	
Intravenous and intramuscular	2	-	-	-	-	1	-	-	-	3	-	1	3	2†	8	
Rupture of membranes	1	-	-	-	-	-	-	-	-	-	-	-	-	1	-	
Total	33	1	27	5	6	4	3	0	5	6	0	1	0	9	74	26

\*F, favorable.

U, unfavorable.

†One patient delivered by cesarean section.

TABLE III. COMPARISON OF DURATION OF LABOR IN FAVORABLE AND UNFAVORABLE CASES (PRIMIPARAS)

METHOD OF INDUCTION	DURATION OF LABOR												PROLONGED LABOR		FAILED INDUCTION		TOTAL CASES	
	2 HOURS OR LESS		2 HOURS, 1 MINUTE, TO 4 HOURS		4 HOURS, 1 MINUTE, TO 6 HOURS		6 HOURS, 1 MINUTE, TO 8 HOURS		8 HOURS, 1 MINUTE, TO 12 HOURS		OVER 12 HOURS		OVER 12 HOURS		OVER 8 HOURS		F	U
	F	U	F	U	F	U	F	U	F	U	F	U	F	U	F	U		
Intravenous	3	-	6	1	6	1	-	1	3	-	-	2	-	-	-	3	18	8
Intramuscular	7	-	15	1	14	2	9	1	8	3	-	-	-	-	-	3	53	10
Intravenous and intramuscular	-	-	-	-	-	-	1*	1	-	2	1	2	-	-	-	3	2*	8
Rupture of membranes	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
Total	11	0	21	2	20	3	10	3	11	5	1	4	0	9	74	26		

\*One patient delivered by cesarean section after 8 hours of labor.

Presumably all cases, on admission, were favorable for induction. Analysis was then undertaken based on the condition of the cervix, whether favorable or unfavorable, and the two groups were compared. Our criteria for a favorable cervix in a primipara are: The cervix must be at least 2 cm. dilated, at least 50 per cent effaced, soft and yielding, and must be anterior; the vertex must be at least at minus 1 station; there should be no cephalopelvic disproportion, and the pregnancy must be judged to be at or near term. On the basis of these criteria, in 74, or 74 per cent, of the primiparas the cervix was favorable for induction and in 26, or 26 per cent, unfavorable.

For the multiparas we adopted different criteria: The cervix must be soft and yielding or "ripe," at least 2 cm. dilated, and partially effaced; the vertex must be at least at station minus 3. On the basis of these criteria, the cervix was favorable for induction in 344 multiparas, or 86 per cent, and unfavorable in 56, or 14 per cent. A comparison of these two groups of cases in both primiparas and multiparas was then undertaken, with special reference to the latent period, duration of labor, rate of complications, and amount of Pitocin used.

### Results

Table I shows a distribution of the cases according to gestation, presentation, and method of induction for both primiparas and multiparas.

#### *Primiparas, 100 Cases.—*

*Latent Period.*—The latent period is defined as the time between the start of the induction, medical or surgical, to the time that regular contractions develop. For the purpose of this study we considered a latent period of over 8 hours as a failed induction, and from 4 to 8 hours as a prolonged latent period.

In 66 per cent of the total of 100 primiparas the latent period was one hour or less, in 13 per cent from 1 to 2 hours, and in 11 per cent from 2 to 4 hours. One patient had a prolonged latent period, and in 9 patients, or 9 per cent, uterine contractions failed to develop and they were sent home undelivered. They later went into spontaneous labor and were delivered normally.

Based on our criteria of "ripeness" of the cervix, it was favorable for induction in 74 primiparas and unfavorable in 26. All patients in whom the cervix was favorable went into labor within 4 hours. Of the 26 patients with an unfavorable cervix, 16, or 61.5 per cent, went into labor within 4 hours; one patient, or 3.9 per cent, had a prolonged latent period, and 9, or 34.6 per cent, failed to go into labor. In Table II the two groups are compared.

*Duration of Labor.*—This is defined as the time from the onset of regular uterine contractions to the delivery of the baby (first and second stages). Of the 100 primiparas, 57 per cent were delivered within 6 hours, and 29 per cent between 6 and 12 hours; 5 per cent had prolonged labor; and 9 per cent failed to go into labor. Thus in 14 per cent of primiparas the result of attempted induction was either absolute failure or unsatisfactory labor.

Of the favorable cervix group, 72 patients, or 97 per cent, were delivered within 12 hours; one patient had a prolonged labor, and another was delivered by cesarean section because of unrecognized cephalopelvic disproportion. Of the unfavorable cervix group, only 13 patients, or 50 per cent, were delivered within 12 hours; four, or 15.3 per cent, had a prolonged labor, and 9, or 34.5 per cent, failed to be delivered following induction. The two groups are compared in Table III.

TABLE IV. COMPARISON OF LATENT PERIOD IN FAVORABLE AND UNFAVORABLE CASES (MULTIPARAS)

METHOD OF INDUCTION	LATENT PERIOD										PROLONGED LATENT PERIOD		FAILED INDUCTION		TOTAL CASES*	
	30 MINUTES OR LESS		31 TO 60 MINUTES		61 TO 90 MINUTES		91 TO 120 MINUTES		121 TO 180 MINUTES		181 TO 480 MINUTES		OVER 8 HOURS			
	F	U	F	U	F	U	F	U	F	U	F	U	F	U	F	U
Intravenous	30	6	22	7	5	1	1	2	1	2	-	1	-	4	59	23
Intramuscular	125	7	105†	11	23	2	14	3	4	1	1	1	-	2	272†	27
Intravenous and intramuscular	1	-	4	2	-	-	3	1	-	-	2	1	-	-	9	5
Rupture of membranes	1	-	2	-	-	-	-	-	-	-	-	-	-	-	3	-
Total	157	13	133	20	28	3	18	6	5	3	1	4	1	6	343	55

\*Does not include the 2 patients delivered by immediate cesarean section before onset of labor.

†Includes one patient delivered by cesarean section.

TABLE V. COMPARISON OF DURATION OF LABOR IN FAVORABLE AND UNFAVORABLE CASES (MULTIPARAS)

METHOD OF INDUCTION	DURATION OF LABOR										PROLONGED LABOR		FAILED INDUCTION		TOTAL CASES*	
	2 HOURS OR LESS		2 HOURS, 1 MINUTE, TO 4 HOURS		4 HOURS, 1 MINUTE, TO 6 HOURS		6 HOURS, 1 MINUTE, TO 8 HOURS		OVER 8 HOURS		OVER 8 HOURS					
	F	U	F	U	F	U	F	U	F	U	F	U	F	U	F	U
Intravenous	13	-	25	7	17	6	4	3	-	3	-	4	-	4	59	23
Intramuscular	90	3	121	9	34	7	22†	3	5	3	-	2	-	2	272†	27
Intravenous and intramuscular	-	-	2	1	5	1	-	-	1	3	1	-	-	-	9	5
Rupture of membranes	-	-	1	-	1	-	1	-	-	-	-	-	-	-	3	-
Total	103	3	149	17	57	14	27	6	6	9	1	6	-	6	343	55

\*Does not include the 2 patients delivered by immediate cesarean section before onset of labor.

†Includes one patient delivered by cesarean section.

*Multiparas, 400 Cases.—*

*Latent Period.*—For multiparas a latent period of from 3 to 8 hours was considered as prolonged and over 8 hours as failed induction. Of the 400 multiparas in the series the latent period was one hour or less in 80.5 per cent; from 1 to 2 hours in 13.75 per cent; and from 2 to 3 hours in 2 per cent; 5 patients, or 1.25 per cent, had a prolonged latent period, and in 7 patients, or 1.75 per cent, regular uterine contractions failed to develop.

Of the 344 patients in whom the cervix was favorable for induction, 340, or 98.55 per cent, went into labor within 3 hours, while one patient had a prolonged latent period, and one failed to go into labor. It is noteworthy that induction failed or was unsatisfactory in only 0.005 per cent of this group.

Of the 56 patients in whom the cervix was unfavorable, 45, or 80.3 per cent, went into labor within 3 hours; 4, or 7 per cent, had a prolonged latent period, and 6, or 10.7 per cent, failed to go into labor. Thus induction failed or labor was unsatisfactory in 17 per cent of this group. The two groups are compared in Table IV.

*Duration of Labor.*—Of the total number of multiparas, 68 per cent were delivered within 4 hours and 25.75 per cent between 4 and 8 hours; 3.75 per cent had prolonged labor, and 1.75 per cent did not go into labor. Three patients were delivered by cesarean section for reasons given below.

The cervix was favorable for induction in 344 patients. Of these, 335, or 97.4 per cent, were delivered within 8 hours; 6, or 1.7 per cent, had prolonged labor; and only one patient, or 0.3 per cent, failed to go into labor. Two patients were delivered by cesarean section, one because of unrecognized disproportion, and the other for premature separation of the placenta.

Of the 56 patients with unfavorable cervixes, 40, or 71.4 per cent, were delivered in 8 hours; 9, or 16 per cent, had prolonged labor, and in 6, or 10.7 per cent, induction of labor failed. One patient was delivered by cesarean section for prolapse of the umbilical cord. The two groups are compared in Table V.

*Quantity of Pitocin Used.—*

Table VI shows the average quantity of Pitocin (expressed in international units) used in this series, by all methods. As might be expected, the patients, both primiparas and multiparas, whose cervixes were unfavorable for induction received a greater average amount of Pitocin than did those with favorable cervixes. Those who were given a combination of intravenous and intramuscular Pitocin received much more Pitocin, on the average, whether the cervix was favorable or not.

TABLE VI. AVERAGE QUANTITY OF PITOCIN USED (IN I.U.)

METHOD OF INDUCTION	PRIMIPARAS			MULTIPARAS		
	ENTIRE SERIES	F	U	ENTIRE SERIES	F	U
Intravenous	4.5	3.1	5.8	3.2	2.6	4.8
Intramuscular	8.4	8.1	11.0	7.0	6.8	9.0
Intravenous and intramuscular	23.0	16.0	25.0	19.0	18.7	19.8

*Complications, Maternal and Fetal.—*

In Table VII are listed the maternal and fetal complications encountered in the entire series.

*Postpartum Hemorrhage.*—Of the 4 cases of postpartum hemorrhage in the primipara group, 3 patients had cervixes unfavorable for induction. The

latent period in all 4 cases was within 3 hours, the duration of labor within 10 hours. The amount of Pitocin used was from 10 to 24 I.U.

Seventeen of the multiparas, or 4.2 per cent, had excessive postpartum bleeding. Twelve of them had received intramuscular Pitocin (average dose, 5 I.U.); 4 intravenous (average dose, 5 I.U.), and one received both, a total dose of 20 I.U. The cervix was favorable for induction in 12 of the 17 patients and unfavorable in 5.

The duration of labor in 8 patients who received intramuscular injections of Pitocin was less than 3 hours (in 4 it was less than 2 hours). The patients who received intravenous Pitocin infusions were all delivered in less than 7 hours. One patient had a labor of 9 hours and 35 minutes. She received 20 I.U. of intramuscular and intravenous Pitocin.

TABLE VII. COMPLICATIONS, MATERNAL AND FETAL

COMPLICATIONS	PRIMIPARAS		MULTIPARAS	
	FAVORABLE CERVIX	UNFAVOR- ABLE CERVIX	FAVORABLE CERVIX	UNFAVOR- ABLE CERVIX
<i>Maternal.—</i>				
Postpartum hemorrhage	1 (1.3%)	3 (11.5%)	12 (3.5%)	5 (9.0%)
Tetanic contraction of uterus	0	1	1	1
Unrecognized disproportion	1	0	1	0
Hematoma	1	0	1	0
Fever (100° F., 1 day)	1	1	5	0
Premature separation of placenta	0	0	1	1
Prolonged labor	1	4	6 (1.74%)	9 (16%)
Thrombophlebitis	0	0	1	0
Mental depression	0	0	1	0
<i>Fetal.—</i>				
Mortality	1*	0	0	1*
Prematurity	1	0	5 (1.25%)	1
Respiratory difficulty	0	3	9 (2.61%)	2 (3.6%)
Atelectasis	0	0	1	0
Prolapsed cord	0	0	0	1
Jaundice	0	0	1	0
Bowel obstruction	1	0	1†	0
Fractured clavicle	0	0	1	0

\*Anencephalic monster.

†Operated on 31 days after delivery.

### Comment

Analysis of this series of 500 cases definitely shows that the most important factor in a successful and safe termination of elective induction of labor is careful selection of patients, with particular reference to the condition of the cervix. Although the criteria for selection of cases will undoubtedly vary somewhat among obstetricians, it is apparent that there is general agreement on what constitutes the minimum requisites for elective induction of labor. The results of this study indicate that the degree of success decreases and the incidence of complications, both fetal and maternal, increases if these criteria are not carefully observed.

In this series there were 16, or 3.2 per cent, failed inductions (9 primiparas and 7 multiparas) of which 15 did not fulfill our criteria of cases favorable for induction. Prolonged labor occurred in 20 instances, or 4 per cent (5 primiparas and 15 multiparas), 13 of which failed to meet our criteria.



There were 21 cases of postpartum hemorrhage severe enough to require blood transfusion (4 primiparas, and 17 multiparas), an incidence of 4.2 per cent. This is approximately twice the over-all incidence of severe postpartum hemorrhage in this hospital. In both primiparas and multiparas the incidence of postpartum hemorrhage was much higher in the group with unfavorable cervixes. In the multiparas a higher incidence of postpartum hemorrhage appeared to be associated with precipitate labor (3 hours or less').

There were 3 cases of tetanic contraction of the uterus, 2 occurring when Pitocin was administered intravenously and one when it was injected intramuscularly. We believe the occurrence of tetanic contractions can be virtually eliminated by rigid adherence to proper technique.

Two patients had premature separation of the placenta, one of whom was delivered by cesarean section.

The gross perinatal mortality in this series is 0.4 per cent and the corrected figure is zero. Prematurity (infant weight 2,500 grams or less) occurred in 7 instances, or 1.4 per cent. Respiratory difficulty was the most common fetal complication, occurring in 14 instances, or 2.8 per cent. All these babies recovered before they were discharged from the hospital. The one case of prolapse of the umbilical cord occurred in a patient with an unfavorable cervix and before full dilatation took place, thus necessitating immediate cesarean section.

### Summary and Conclusions

1. An analysis of 500 consecutive cases of elective induction of labor done at the Millard Fillmore Hospital from Jan. 1, 1956, to Feb. 28, 1957, is presented.
2. There was no maternal mortality; the corrected fetal mortality is zero.
3. Elective induction of labor can be performed successfully and safely, and with a minimum of complications, if strict adherence to proper criteria for selection of cases is observed. Misuse and abuse of Pitocin can easily lead to fetal as well as maternal complications.

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## CASTOR OIL AS AN ADJUNCT TO INDUCTION OF LABOR: CRITICAL RE-EVALUATION

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CASTOR oil employed for the induction of labor has been popular for over a century although a report of the first use in this connection was not available. Castor seeds were known from the time of the ancient Egyptians, but castor oil did not appear in materia medica until Dr. Peter Cavane of England published a dissertation on the subject in 1764.<sup>1</sup> Sixty-two years later in 1826, Dewees<sup>2</sup> mentioned the belief that castor oil had some abortifacient or oxytocic properties. Labor was not commonly induced during the eighteenth and nineteenth centuries and the influence of castor oil was not dwelt upon in the textbooks of those eras. In 1871 Frederick Porter Smith<sup>3</sup> wrote under a heading of "Castor Oil Seeds," "The pulp is rubbed into the soles of parturient women to hasten the birth of the child, or the expulsion of the placenta." John King<sup>4</sup> in 1874 described nine methods of inducing labor, but made no mention of castor oil. Likewise, Barton Cooke Hirst's<sup>5</sup> book of 1903 made no mention of castor oil for induction of labor. In 1910, Jardine,<sup>6</sup> discussing induction of labor, wrote, "The bowel should be cleared by means of laxative medicine and enema." He did not specifically suggest castor oil. In 1941, Goodman and Gilman<sup>7</sup> stated, "In many cases, a cathartic is all that is necessary to initiate uterine activity. Castor oil in 30 to 60 cc doses is often employed for this purpose. The cathartic has no direct effect on the uterus, but apparently the organ is reflexly stimulated as a result of pelvic vascular congestion and the intestinal irritation."

Particularly since 1920, when Watson<sup>8</sup> described his induction methods, many obstetricians have used castor oil. Although Watson wrote primarily about the use of pituitary extract, he included castor oil in his routine and so have most writers on the subject since then.<sup>9-13</sup> As to its efficacy, Hewitt and others<sup>13</sup> said, "Of the four agents employed in Watson's technique, pituitrin is probably the most potent in stimulating uterine contractions, but the castor oil may be an important auxiliary. In this connexion it is interesting to note the frequent administration and the generous dosage of castor oil meted out by the nursing staff in the ante-natal department where the wards are overcrowded."

### Method

In order to evaluate the efficacy of castor oil when employed as an adjunct to induction of labor two approaches were used: (1) a questionnaire study,

(2) a clinical experiment. An attempt was made to determine approximately how popular the use of castor oil is today for the induction of labor. A questionnaire was sent to heads of the Departments of Obstetrics of 50 medical schools in the United States and 32 were returned. Of the 32 reporting, 16 never employ castor oil for inducing labor, but 16 use it some of the time.

Clinically, 114 consecutive inductions of labor at Parkland Hospital from 1952 through 1954 were studied. The inductions were routinely carried out with rupture of the membranes and Pitocin. In most instances, the Pitocin was given by intermittent intramuscular injection, but occasionally an intravenous drip was used. The patients were divided into four groups as follows:

1. Rupture of membranes and Pitocin
2. The same plus enema
3. The same with castor oil instead of enema
4. The same with addition of both castor oil and enema

Patients were automatically and successively rotated among the four groups.

In each group the Pitocin was given by starting with 1 minim and increasing the dosage every half hour by an additional minim until labor was established. Never more than 6 minims were given at any one dose. When a dosage of 6 minims had been reached and repeated twice, if the patient was not in labor, the induction was discontinued, considered to have failed, and repeated the following day.

The majority of our inductions were considered obligatory. In other words, there was a definite obstetric indication for instituting labor (Table I). In many cases, the mother was neither at term, nor was the cervix considered "ripe." A tabulation of infants' weights showed an equal distribution throughout the four groups. The differences in the average dose of Pitocin required in each group were not significant.

TABLE I. INDICATIONS FOR INDUCTION

	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Pre-eclampsia	8	8	9	8
Hypertension	8	7	12	12
Ruptured membranes	5	6	5	4
Elective	0	4	3	6
Postmaturity	2	1	3	1
Rh-isoinmunization	1	0	0	0
Abruptio placentae	0	1	0	0
	24	27	31	32

The length of the labors is shown in Table II.

TABLE II. LENGTH OF LABORS

LENGTH OF LABOR	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	HOURS	MINUTES	HOURS	MINUTES	HOURS	MINUTES	HOURS	MINUTES
Shortest		54		50		23		60
Longest	10	54	8	3	10	20	10	41
Average	4	42	2	54	4	12	4	18

There were 5 failures each in Groups 1, 2, and 4, and 3 failures in Group 3. In 6 of the 18 failures, cesarean section was performed and the remainder of these patients were delivered vaginally after reinduction on the following day.

These data indicate that in a small unselected series of inductions, only two factors are important; ruptured membranes and Pitocin. Although an empty bowel is desirable for labor and delivery, our experience suggests that the enema alone accomplished this result satisfactorily.

We feel that on the basis of these data castor oil is of no value in the induction of labor. It is an irritating medicine and of some cost to the patient. Indeed, one can agree with the postscript on our questionnaire returned from the professor of a leading university who wrote: "A dehydrating, debilitating, drastic drug; it should be used on machinery only."<sup>14</sup>

### Conclusions

1. Castor oil seems to have come into use in induction of labor without specific value.
2. In a small controlled series of inductions, castor oil did not influence the inductions.
3. For cleansing the bowel, an enema is adequate, easy, and inexpensive.
4. The use of castor oil in inductions of labor is unnecessary.

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## THE INTRAVENOUS USE OF DEMEROL, SCOPOLAMINE, AND NALLINE IN LABOR

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THE search for an ideal analgesic in obstetrics is constant. Many drugs have been advocated, tried, and discontinued. If women were able to endure labor without analgesia or anesthesia, few infants would be depressed at birth. However, the overwhelming majority need and deserve as much help as possible.

For years meperidine (Demerol) has been used for this purpose, either intramuscularly or intravenously. The incidence of neonatal depression following the use of this drug has been variously reported to be from 8 to 16 per cent.<sup>1-5</sup> The statistics differ because of different methods of evaluation of the infant and the anesthesia used. Lasagna and Beecher<sup>6</sup> have reported quantitative data on the depressant effect of meperidine on the respiratory center. Their results negate previous claims that this drug is devoid of respiratory hazards. Rosenfeld and associates<sup>7</sup> used Demerol and scopolamine by continuous intravenous drip on 123 patients. Eight infants were slightly cyanotic and only 6 (5 per cent) required resuscitation. One baby died of congenital heart disease.

N-allyl-normorphine (Nalline) apparently counteracts the respiratory depression caused by morphine and Demerol. Eckenhoff and co-workers<sup>8</sup> gave 10 mg. of Nalline intravenously prior to delivery with good results. Barr and Barr<sup>9</sup> noted that the administration of Nalline to the mother produced a significant reduction in the interval between delivery and the onset of respiratory efforts compared with the interval in a control group. Fourteen per cent of the control babies required resuscitative measures, whereas only 6 per cent of those whose mothers received Nalline needed this aid. Nalline with morphine has been given intramuscularly during labor and also alone via the umbilical vein to the depressed infant. Cappe, Himel, and Grossman<sup>10</sup> advocated the use of a mixture of morphine and Nalline intravenously in divided doses during labor. We were impressed by the use of meperidine, scopolamine, and N-allyl-normorphine during labor in a small series of private cases and decided to check this impression on a larger group of patients.

### Method

When labor was established, 5 per cent glucose in water was started intravenously. A mixture containing 100 mg. of Demerol, 0.3 mg. of scopolamine, and 10 mg. of Nalline was drawn up into a 10 c.c. syringe. When the patient



asked for sedation, one-third to one-half of this solution was slowly injected through the intravenous tubing. This was repeated at intervals of 10 minutes or more until the desired effect was obtained, regardless of the imminence of delivery. Pitocin was frequently used in these cases, but our results with this drug have been previously reported.<sup>11</sup> The patients were evaluated subjectively and objectively for pain relief. The infants were checked either by the time of onset of sustained crying, or by the Apgar<sup>12</sup> classification one minute after delivery. We found that the time of onset of sustained crying was as satisfactory as the Apgar scale and the latter will only be mentioned for those babies for whom resuscitative measures were necessary. Contributing causes or associated factors for the infant depression were also investigated.

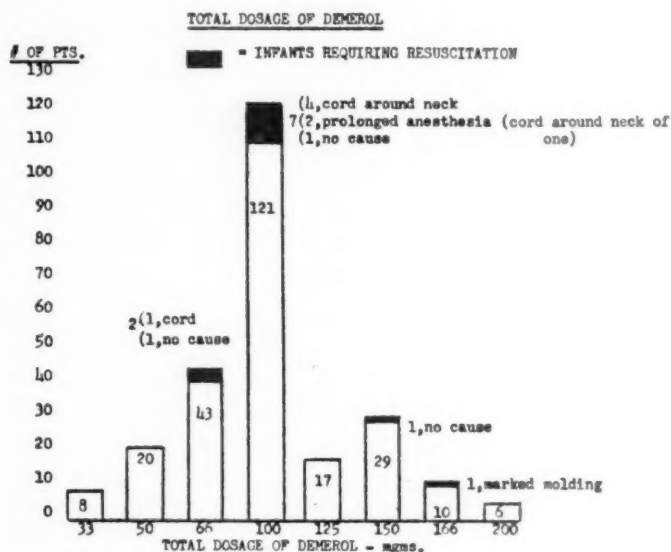


Fig. 1.

### Material

A total of 265 patients received Demerol, scopolamine, and Nalline during labor; 222 were private and 43 were service cases. The ages varied between 15 and 44 years. The duration of the pregnancies ranged from 34 to 45 weeks. Labor was electively induced in 40 cases and a total of 213 received Pitocin. There were 95 primiparas and 170 multiparas; 178 patients were delivered spontaneously, 80 by elective forceps, 4 by indicated midforceps, and 3 by partial breech extraction; 251 patients were given nitrous oxide, oxygen, and Trilene inhalation anesthesia, supplemented by perineal or pudendal novocaine block, 4 had saddle block, and 5 had no anesthesia.

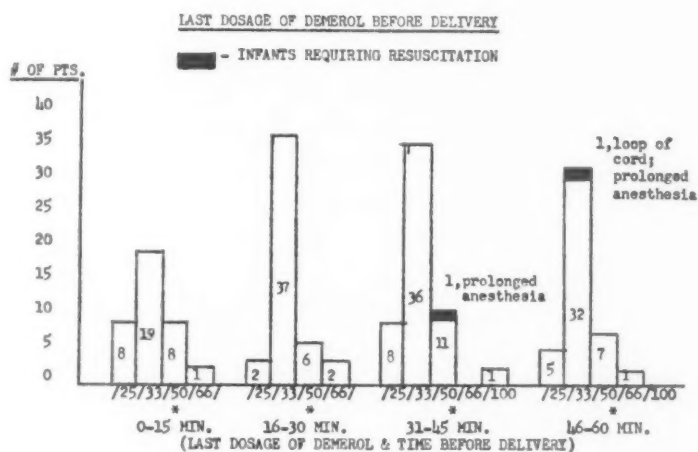
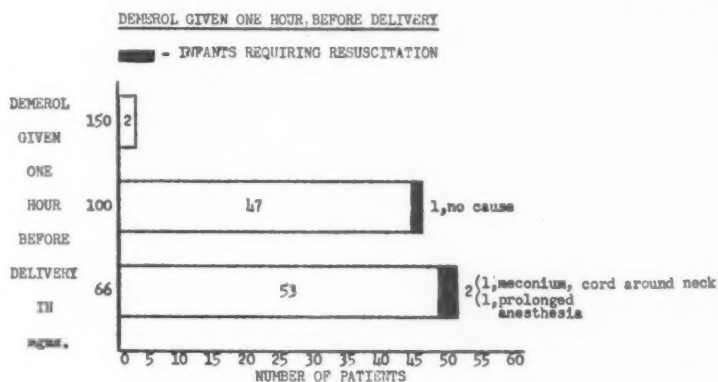
### Results

In 190 patients (72 per cent) the first stage of labor lasted less than 10 hours. Pain relief was evaluated as noted in Table I.

In this series 254 infants (95.8 per cent) cried in a sustained manner within one minute after delivery. Eleven (4.2 per cent) infants required resuscitation and responded in 2 to 4 minutes. None of these babies was markedly depressed (only 3 below Apgar 7), and there were no deaths. The associated factors noted in the depressed babies appear in Table II.

TABLE I. PAIN RELIEF

	NO. OF CASES	%
<i>Subjective Relief.</i> —		
Excellent	206	77.7
Good	55	20.7
Fair	4	1.6
<i>Objective Relief.</i> —		
Excellent	221	83.4
Good	37	13.9
Fair	7	2.7



The minimum total dosage of Demerol was 33 mg. and the maximum 200 mg. (Fig. 1). One hundred two patients received 66 mg. of Demerol or more within one hour prior to delivery.

There were 3 slightly depressed infants (Apgar 8) in a series of 102 patients who received 66 mg. of Demerol or more within one hour prior to delivery (Fig. 2).

The patients were further evaluated according to the time interval between the last dose of the mixture and delivery (Fig. 3). There were only 2 depressed babies noted (Apgar 7 and 8).

An irritative excessive cry was noted in 14 cases. The cause and significance of this phenomenon are not known.

TABLE II. ASSOCIATED FACTORS IN DEPRESSED INFANTS

Cord around neck	6
Marked molding	1
Prolonged anesthesia (1 included under "cord around neck")	2
Prematurity (2,000-2,500 grams)	1
No contributing cause	2
Total no. requiring resuscitation	11 or 4%

### Conclusions

1. A mixture of Demerol, scopolamine, and Nalline in the amounts and proportions noted may be given intravenously with relative safety to both mother and child.

2. Demerol, scopolamine, and Nalline may be given with adequate relief to the mother and without undue depression of the infant.

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## THE PROBLEM OF SPONTANEOUS ABORTION\*

### V. The Genesis of Spontaneous Abortion

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THE presence of collagen plaques and fibrinoid necroses in the placental villi in the majority of cases of spontaneous abortion<sup>1, 2, 3</sup> suggested a histological analogy to the soft tissue lesions of rheumatoid arthritis. In the latter disease the observation that blood serum in established active cases will agglutinate sheep red blood cells has been turned to good account, being now the foundation of a diagnostic test. The ability of serum to agglutinate sheep red cells is, however, not restricted specifically to rheumatoid arthritis for the serum in other "collagen diseases" also gives positive results. On the basis of the histological evidence suggestive of "collagen disease" in the placental villi, we felt that it would be in logical sequence to examine the serum from women suffering from spontaneous abortion for the agglutinating substance.

#### Material and Methods

Blood was collected from unmarried healthy women, from women at the third month of an apparently normal pregnancy, from those at full term, and from those who suffered spontaneous abortion at the time of abortion. The first three groups acted as controls for the last. The serum obtained from the blood was titrated for agglutinating properties with the use of the Rose-Waaler test as modified by Greenbury.<sup>4</sup> It was subsequently altered by us and eventually used as follows:

The serum under test was inactivated at 56° C. for 30 minutes, then serially diluted from 1:2 to 1:256 in twofold steps in sterile normal saline. Four sets of dilution were made for each sample of serum in 10 by 75 mm. tubes. To the first row was added 1 volume of 1 per cent thrice-washed sheep cells; this was a control. To the second was added 1 volume of 1 per cent sheep cells sensitized with the maximum possible amount of rabbit anti-sheep cell serum; this was the test row. To the third 1 volume of 1 per cent sheep cells suspended in 7 per cent placental extract in normal saline was added; this was the control absorption row. The final row contained 1 volume of 1 per cent sensitized cells suspended in the same vehicle as in the absorption control; this was the absorption test row. With each set a control tube consisting of 1 per cent washed sheep cells in a volume of normal saline was added.

The placental extract consisted of fresh human placenta washed in running water, dried, then emulsified in a Waring Blender at a concentration of

\*This work was supported by a Federal Health Grant.

25 Gm. of tissue to 100 ml. of saline. It was then filtered to remove debris and the filtrate passed through a Seitz filter for sterility. The extract was then ready for use.

The completed test was incubated for 1 hour at 37° C., then left at 10° C. overnight and read the following morning. The same number of finger taps needed to resuspend the red cells in the saline control were applied to each tube in the set. In the lower titers this treatment resulted in a solid clump of cells which, as the dilutions progressed, passed into fine granular aggregates, then sharply into a smooth suspension. The end point was the last tube showing the granular state. Titers of 1:16 or more were taken as positive provided that the control row end point multiplied by 4 was not greater than the test reading. That is to say, a control giving agglutination at a dilution of 1:2 or 1:4 allowed for a test of 1:16 and up as positive. If, however, the control was 1:8 the test would then have to be 1:32 to be acceptable for inclusion as a positive result.

The remainder of the serum was used for what we have termed the latex flocculation test. This is a modification of Plotz and Singer's latex fixation test.<sup>5</sup> The serum was serially diluted in boric acid-sodium hydroxide-saline buffer from 1:200 to 1:1,250 in 12 by 75 mm. test tubes. To each tube was added 1 volume of a mixture of 1 per cent polystyrene latex and 5 per cent placental extract in saline. The test was incubated for at least 2 hours at 56° C. or preferably overnight and read the following morning, the tubes being smartly tapped to suspend their contents. The reaction which occurs is complex and it is being reported in detail elsewhere. It seems, however, that tissue extract made in the manner already described for that obtained from the placenta contains a protein that is denatured at 56° C. when heated for at least 2 hours. On denaturation large floccules are formed which bring the latex out of its colloidal state to produce "snowflake-like" particles. Albumin and gamma globulin inhibit floccule formation, but this is not grossly quantitative for we have found that the depression of denaturation coincides more closely with total gamma globulin antibody activity than with serum protein levels. In the test as outlined, the first tube showing large "snowflakes" was taken as the end point, the normal range being from 1:200 to 1:500.

The placentas obtained from the cases of abortion were fixed in formalin and stained by hematoxylin and eosin, Masson's trichome, and toluidine blue.

### Results

The titers obtained from the sera of 10 healthy unmarried women between the ages of 18 and 35 examined by the modified Rose-Waaler and latex flocculation tests are shown in Table I.

TABLE I. THE MODIFIED ROSE-WAALER AND LATEX FLOCCULATION TEST TITERS IN UNMARRIED HEALTHY WOMEN

NO.	ROSE-WAALER		ROSE-WAALER + PLACENTAL EXTRACT		LATEX FLOCCULATION
	C*	T*	C*	T*	
1	1:4	1:8	1:4	1:4	1:300
2	1:4	1:4	1:4	1:4	1:300
3	1:2	1:4	1:2	1:4	1:400
4	1:2	1:4	1:2	1:4	1:300
5	1:4	1:8	1:4	1:8	1:400
6	1:4	1:8	1:4	1:8	1:300
7	1:2	1:4	1:2	1:4	1:500
8	1:4	1:8	1:4	1:8	1:500
9	1:2	1:4	1:2	1:4	1:400
10	1:2	1:4	1:2	1:4	1:300

\*C, unsensitized cell row. T, sensitized cell row.



In Case 1 of Table I there is a very moderate increase in agglutination in the Rose-Waaler test over the control, a moiety which is absorbed by the placental extract. Otherwise the series shows the regular monotony of normality. It is presumed that the basic agglutination seen in this test is due to nonspecific antibody and the sensitization of the sheep cells in the test row is responsible for the slightly higher readings than those which occur in the nonsensitized.

The sera from 20 healthy pregnant women were next examined. The specimens were taken just before and just after labor. The results are shown in Table II.

TABLE II. THE MODIFIED ROSE-WAALER AND LATEX FLOCCULATION TEST TITERS IN 20 HEALTHY WOMEN AT TERM

NO.	ROSE-WAALER		ROSE-WAALER + PLACENTAL EXTRACT		LATEX FLOCCULATION
	C	T	C	T	
1	1:4	1:8	1:4	1:4	1:300
2	1:4	1:8	0	1:2	1:300
3	1:2	1:8	1:2	1:2	1:400
4	1:2	1:4	0	1:2	1:400
5	1:4	1:8	1:4	1:8	1:400
6	1:4	1:8	1:2	1:4	1:300
7	1:4	1:8	1:4	1:4	1:500
8	1:4	1:8	1:2	1:4	1:300
9	1:2	1:4	1:2	1:2	1:400
10	1:2	1:4	1:2	1:4	1:300
11	1:2	1:4	0	1:2	1:300
12	1:2	1:4	1:2	1:4	1:400
13	1:4	1:8	1:2	1:2	1:500
14	1:2	1:4	0	1:2	1:400
15	1:2	1:4	1:2	1:2	1:400
16	1:4	1:8	1:4	1:4	1:500
17	1:2	1:4	0	1:2	1:300
18	0	1:2	0	1:2	1:300
19	1:2	1:4	0	1:2	1:300
20	1:2	1:8	1:2	1:4	1:500

The findings in Table II parallel those in unmarried healthy women except in one respect. In 16 cases out of the 20 a small amount of absorbable agglutinating substance was found but in no case did the titer reach pathological levels.

The next step was to examine the sera of women in the first trimester of pregnancy. It is impossible at such an early stage to forecast whether or not any conception will be stable, but, within the limits imposed by clinical evidence, reasonably suitable cases were selected for the titration of their serum antibodies. The results are shown in Table III.

Cases 4, 10, 17, and 23 in Table III show pathological Rose-Waaler titers. In the first 3 there was considerable absorption of the agglutinating substance by the placental extract. In Cases 10, 17, and 23 the latex flocculation was normal.

In Case 4 the table shows the findings as on Jan. 24, 1957. The subsequent course was as follows:

March 2, 1957	Threatened abortion. Bed rest
March 6, 1957	RW: C = 1:2 T = 1:16
	RW + P: C = 1:2 T = 1:4
	Latex: 1:800
March 30, 1957	Pregnancy maintained
	RW: C = 1:2 T = 1:8
	RW + P: C = 1:2 T = 1:4
	Latex: 1:300

In Case 10 the serum showed the titer given in the table on Nov. 3, 1956. On Dec. 14, 1956, the patient started to bleed and abortion was considered inevitable. On bed rest, however, the patient settled down. On April 30, 1957, her titers were as follows:

RW: C = 1:8 T = 1:64  
Latex: 1:1,000

The pregnancy still continues.

Case 17 had an abortion within 10 days of the finding of a pathological titer; she would not return to hospital for further examination. For Case 23 we have no explanation, but the agglutinating substance appears to differ from the three previous in that it is not absorbed by placental extract. We can only suggest that the increased titer is a response to some condition other than abortion or "collagen disease." It will be noted that 15 of the remaining cases showed a moiety of absorbable agglutinating substance as did the normal full-term controls.

Table IV shows the findings in 40 cases of spontaneous abortion. A summary of the findings is as follows:

1. Increased titer in the Rose-Waaler and/or an increase in latex flocculation titer associated with collagen lesions in the villi	29
2. Normal serological titers and normal villi (2 of these were blighted ova and 1 a case of abruptio placentae)	7
3. Rose-Waaler and latex titer normal, histologically collagenized villi	1
4. Raised titer of Rose-Waaler and latex; histologically hydatidiform degeneration	1
5. Rose-Waaler and latex raised, histologically normal	1
6. Latex titer only raised (This was a case of complete placental infarction)	1
	<hr/> 40

Of the 40 cases, 30 showed changes in the villi of the collagen type, and in 29 this was reflected by an increase in serum "antibodies." In the remainder, 5 were associated with other placental lesions or blighted ova, and one of these—that of the hydatidiform degeneration—showed an increased titer by the Rose-Waaler and latex flocculation tests. There was one false serological positive and in this and the other 4 cases which were normal histologically and serologically we have no explanation for the abortion.

Twelve of the 40 women had a history of abortion in previous pregnancies and in 8 of these the "antibody" titers were raised. Only one of the 12, however, had normal placental villi.

Examination of the Rose-Waaler titers in the 40 cases shows, first, that there appears to be very little relationship between the height of the titer and histological activity and, second, that most of the antibody is absorbed by placental extract. This same phenomenon was noted in the pregnant controls, but as the amounts are considerably larger in abortion the steep drop in the titer brought about by the exhibition of the extract is much more striking.

#### Experiments With the Sensitized Sheep Red-Blood-Cell-Agglutinating Substance

It seemed essential to compare the agglutinating substance found in the sera from cases of rheumatoid arthritis with that from abortion. Consequently a series of absorption experiments were carried out to see if they were similar or dissimilar substances. Sera from cases of rheumatoid arthritis,

abortion, and infectious mononucleosis—the latter containing heterophil antibody—were put against placental extract, guinea pig kidney extract, and ox red-blood-cell extract. The terms of the experiments were the same as already described for the absorption row in the Rose-Waaler technique. The results are shown in Table V.

TABLE III. THE MODIFIED ROSE-WAALER AND LATEX FLOCCULATION TEST TITERS IN 24 WOMEN IN THE FIRST TRIMESTER OF PREGNANCY

NO.	ROSE-WAALER		ROSE-WAALER + PLACENTAL EXTRACT		LATEX	REMARKS
	C	T	C	T		
1	1:2	1:4	0	1:2	1:400	
2	1:2	1:4	0	1:2	1:400	
3	1:2	1:4	1:2	1:2	1:400	
4	1:8	1:32	1:4	1:16	1:1,000	Rh negative. Became a case of threatened abortion. See text
5	1:2	1:8	1:2	1:4	1:300	
6	1:2	1:8	0	1:4	1:500	
7	1:4	1:4	1:2	1:4	1:300	Rh negative. Delivered of normal twins
8	1:2	1:4	0	1:2	1:400	
9	1:2	1:4	0	1:2	1:500	
10	1:4	1:32	1:2	1:8	1:500	Considered an inevitable abortion at one stage. See text
11	1:2	1:2	0	1:2	1:500	
12	1:2	1:8	0	1:2	1:400	
13	1:2	1:4	0	1:2	1:300	
14	1:2	1:4	1:2	1:2	1:400	
15	1:4	1:8	1:4	1:8	1:300	
16	1:2	1:2	1:2	1:2	1:400	Rh negative
17	1:8	1:32	1:8	1:8	1:300	Abortion 10 days after serum examination
18	1:2	1:4	0	1:2	1:400	
19	1:2	1:4	1:2	1:2	1:300	
20	0	1:4	0	1:2	1:500	
21	1:4	1:8	1:2	1:4	1:500	
22	1:4	1:8	1:2	1:4	1:500	
23	1:8	1:32	1:8	1:32	1:500	RW titers checked 7 days later C = 1:8 T = 1:16 C = 1:8 T = 1:16
24	1:8	1:8	1:4	1:8	1:800	

It will be seen that the agglutinating substance in the sera of rheumatoid arthritis and of abortion follows the same absorption pattern, while the heterophil antibody from cases of infectious mononucleosis differs in that it is not absorbed by placental extract, weakly by guinea pig kidney, and strongly by ox blood cells. It is reasonable to conclude therefore that the agglutinating factor in abortion and rheumatoid arthritis is the same.

Attention was now turned to the behavior of the placental extract as an antigen. Three full-grown rabbits, 1 male and 2 female, were selected for the experiment. Blood removed from the ear vein of each was titrated for agglutinating substance by the Rose-Waaler technique and for inhibition of flocculation by the latex test. Each rabbit then received 1 ml. of placental extract intramuscularly at weekly intervals for 3 weeks. They were bled on the twenty-sixth day of the experiment and the serum titrations repeated.

The results are shown in Table VI.

There is no doubt that the placental extract can act as an antigen and its antigenic power can be measured by the presence of agglutinating substance as

TABLE IV. THE MODIFIED ROSE-WAALER AND LATEX FLOCCULATION TEST TITERS IN SPONTANEOUS ABORTION

NO.	ROSE-WAALER			ROSE-WAALER + PLACENTAL EXTRACT			LATEX	PLACENTAL VILLUS HISTOLOGICAL CHANGES	REMARKS
	C	T		C	T				
1	1:4	1:128		1:2	1:16		1:1,000	Villi show marked metachromasia	5 months later titers and latex normal. Primipara
2	1:4	1:8		1:4	1:8		1:500	Normal villi	Previously 2 full-term and one abortion
3	1:4	1:16		1:2	0		1:1,600	Villi at stage of collagenous proliferation	1 full-term baby, 1 abortion, then 2 full-term. This pregnancy, twins
4	1:8	1:32		1:4	1:4		1:2,500	Villi markedly metachromatic	4 previous pregnancies normal
5	1:4	1:16		1:2	1:2		1:1,600	Villi at stage of collagenous proliferation	2 full-term. Last pregnancy aborted
6	1:8	1:128		1:4	1:32		1:800	Villi at stage of hyalinization	3 full-term, 2 abortions previously
7	1:4	1:16		1:4	1:4		1:1,000	Villi at stage of collagenous proliferation	3 full-term, then 2 abortions, then 3 full-term
8	1:4	1:16		1:4	1:4		1:600	Villi at stage of fibrinoid necrosis	3 previous full-term
9	1:4	1:16		1:2	1:4		1:800	Villi at early collagenous proliferation	Primipara
10	1:2	1:16		1:2	1:4		1:1,200	Villi show focal fibrinoid necrosis	4 previous normal pregnancies
11	1:4	1:16		0	1:2		1:800	Most villi normal, rest show fibrillary proliferation	1 previous normal pregnancy
12	1:2	1:2		1:2	1:2		1:500	Normal villi	1 previous abortion
13	1:2	1:8		1:2	1:8		1:400	Normal villi	Primipara
14	1:2	1:8		1:2	1:2		1:1,000	Placenta completely infarcted	1 previous pregnancy
15	1:4	1:16		0	1:2		1:800	Villi completely collagenized	2 previous normal pregnancies, 1 abortion
16	1:8	1:32		1:8	1:8		1:1,200	Villi at proliferative stage	2 previous abortions. No successful pregnancies
17	1:8	1:16		1:4	1:8		1:600	Gross hemorrhage, scattered villi	5 previous normal pregnancies
18	1:4	1:32		1:2	1:4		1:1,000	Proliferation of Hofbauer cells and collagen proliferation	Primipara

19	1:2	1:8		0	1:4		1:400	Abruptio placentae	Primipara
20	1:4	1:8		1:8	1:8		1:800		

18	1:4	1:32	1:2	1:4	1:400	Abruptio placentae	Primipara
						Many villi show complete collagenization	4 full-term and 2 previous abortions
19	1:2	1:8	0	1:4	1:400	Scattered villi show fibrinoid necrosis	Patient suffered from sarcoid. Previous abortions
20	1:4	1:8	1:2	1:2	1:1,200	Villi show gross collagenization	3 full-term pregnancies previously
21	1:4	1:8	1:2	1:2	1:500	Villi show collagen proliferation	Primipara
22	1:16	1:64	1:8	1:16	1:1,000	Normal placenta	Blighted ovum
23	1:8	1:32	1:4	1:8	1:1,000	Villi completely collagenized	2 previous normal pregnancies, 4 months later titers normal
24	1:4	1:8	1:2	1:2	1:400	Scattered villi show fibrinoid necrosis	1 previous normal pregnancy
25	1:4	1:64	1:2	1:4	1:1,000	Villi show collagenous proliferation	5 full-term and 2 previous abortions
26	1:4	1:4	1:2	1:2	1:500	Villi show marked fibrinoid necrosis	3 previous normal pregnancies
27	1:4	1:16	1:4	1:4	1:400	Villi at proliferative stage	Primipara
28	1:2	1:64	1:2	1:4	1:1,200	Villi at metachromatic and early proliferative stages	1 previous normal pregnancy
29	1:2	1:16	1:2	1:4	1:800	Villi at proliferative stage	1 previous full-term baby
30	1:2	1:32	1:2	1:4	1:1,000	Normal villi	5 previous normal pregnancies
31	1:16	1:64	1:8	1:16	1:500	Villi show proliferative and fibrinoid necrotic changes	Primipara
32	1:2	1:16	1:2	1:4	1:1,000	Villi show proliferative and fibrinoid necrotic changes	2 previous full-term pregnancies
33	1:2	1:8	1:2	1:4	1:600	Metachromasia	1 full-term and 1 ectopic pregnancy and 2 abortions previously
34	1:2	1:4	1:2	1:2	1:800	Marked collagenous proliferation	Primipara
35	1:8	1:32	1:2	Insufficient	1:600	Hydatidiform degeneration	
36	1:2	1:16	0	1:4	-----	Normal villi	Blighted ovum. 2 previous normal pregnancies
37	1:4	1:16	1:2	1:4	1:800	Marked collagenous proliferation	2 previous normal pregnancies, titer 6 weeks later normal
38	1:2	1:8	1:2	1:4	1:500	Hyalinization of villi	Primipara
39	1:2	1:16	1:4	1:4	1:500		
40	1:4	1:16	1:2	1:4	1:500		



shown by the Rose-Waaler test, placental extract absorption, and latex flocculation inhibition. Experimentally, it has been possible to produce serological changes in rabbits similar to those seen in man in rheumatoid arthritis and abortion.

It is accepted that a serum globulin of 4 Gm. per cent or over is often associated with "collagen" disease. In spontaneous abortion the collagen changes are restricted to the fetal and placental parts and there appears to be no reason to suspect that the maternal serum would reflect, by a rise in its globulin content, what might be taking place in the fetal plasma. In order to check this assumption, we measured the maternal globulin in 21 cases of spontaneous abortion and, in all, the levels were within normal limits, ranging from 2.0 to 3.1 Gm. per cent.

TABLE V. ABSORPTION EXPERIMENTS ON SERA FROM CASES OF RHEUMATOID ARTHRITIS, ABORTION, AND INFECTIOUS MONONUCLEOSIS

DISEASE	ORIGINAL TITER	TITER AFTER ABSORPTION AGAINST		
		PLACENTAL EXTRACT	OX CELLS	GUINEA PIG KIDNEY
1. Rheumatoid arthritis	1:128	1:16	1:4	1:16
2. Abortion	1:64	1:4	1:4	1:16
3. Infectious mononucleosis (convalescent)	1:64	1:64	0	1:32
4. Rheumatoid arthritis	1:64	1:4	1:8	1:2
5. Abortion	1:64	1:8	1:8	1:16
6. Infectious mononucleosis	1:1,280	1:1,280	1:8	1:640
7. Pooled abortion serum	1:32	1:8	1:2	1:4
8. Pooled rheumatoid arthritis serum	1:32	1:8	1:2	1:2
9. Rheumatoid arthritis serum	1:32	1:4	1:2	1:2

TABLE VI. EXAMINATION OF RABBIT SERA BY THE ROSE-WAALER AND LATEX FLOCCULATION TESTS BEFORE AND AFTER PLACENTAL EXTRACT IMMUNIZATION

NO.	ROSE-WAALER		ROSE-WALLER + PLACENTAL EXTRACT		LATEX
	C	T	C	T	
<i>Before Immunization.—</i>					
1	1:4	1:8	1:4	1:8	1:400
2	1:2	1:8	1:4	1:8	1:300
3	1:2	1:4	1:2	1:4	1:800
<i>After Immunization.—</i>					
1	1:2	1:64	0	1:8	1:1,600
2	0	1:16	0	0	1:1,200
3	1:2	1:128	0	1:8	1:1,000

### Comment

It is a bizarre proposition that two diseases with such divergent clinical pictures as spontaneous abortion and rheumatoid arthritis appear to unite as a pathological entity. However, the histological lesions are similar, the serological response to the disease process the same, and the "antibody" absorption phenomenon identical. Thus the concept of etiological unity seems reasonably sound and any attempt at dichotomy must offer a suitable explanation for this parallelism in observations.

There has been considerable discussion revolving around the substance in the serum of rheumatoid arthritis that agglutinates sensitized sheep red

blood cells. Heller<sup>7</sup> considers it an antibody, Lospalluto and Ziff<sup>8</sup> have shown that this component lies in the gamma globulin range and have isolated an inhibitory factor to hemagglutination in normal human serum. Smyth and Clark<sup>9</sup> have demonstrated an intimate relationship between the agglutinating gamma globulin and polysaccharide. Greenbury has shown that polysaccharide acts as a specific antigen by elution experiments.

Our observations offer further confirmation that the agglutinating factor is an antibody. First, we have measured the rise in antibody titer in rabbit serum after inoculation with an antigenic substance; second, the latex flocculation titer ran *pari passu* with the Rose-Waaler in most cases of spontaneous abortion; and, third, the sera obtained from postabortion cases showed a reversion to normal after removal of the stimulus. Further, we would subscribe to Greenbury's<sup>10</sup> suggestion that the specific antigen is polysaccharide for we have noted that the earliest change in the diseased villi of abortion is gamma metachromasia in the ground substance.

It is doubtful that the substance which inhibits agglutination in placental extract is an antigen. It appears to be nonspecific, for we have demonstrated its occurrence in extracts of human liver and the supernatants derived from guinea pig and ox red blood emulsions. It seems more likely to be allied to Lospalluto and Ziff's serum inhibitory factor. The presence of such a substance in the tissue and serum of normal pregnant women would offer an explanation for the lack of demonstrable placental histopathological changes in spite of the presence of small amounts of free agglutinable antibody in their serum.

Based on the work of others and our own observations, we suggest that the following hypothesis might be tenable as an explanation for what happens in spontaneous abortion and the positive Rose-Waaler reaction. Polysaccharide from the ground substance of the placental villi passes through the epithelium into the mother's blood stream, and, acting as a specific antigen, stimulates the lymphoreticuloendothelial system to produce an antibody of a divalent type. A portion of antibody is absorbed by antigen in its passage through the maternal vascular tree; the remaining free antibody is available to react with sensitized sheep cells coated with unbound antigen; and the divalent antibody then binds adjacent red-cell-receptor sites together. The fetal tissue is protected from an antibody-antigen reaction occurring within the ground substance by the presence of a nonspecific inhibitor which blocks one or other component. In spontaneous abortion the lack of inhibitor allows for the increased manufacture of free antibody following antigenic stimulation, the antibody then enters into the ground substance of the villus where a tissue antibody-antigen reaction takes place. This union within tissue is accompanied by the formation of acid mucopolysaccharide whose production is followed by collagen proliferation. This, of course, does not answer the obvious question as to what governs the demand for inhibitor and why in one

pregnancy a conception goes to term and in the next abortion at the second or third month occurs, both in the same woman. Further speculation along this line at the present would be futile.

We suggest on the evidence presented that autoimmunization as a factor in the causation of collagen disease receives considerable support from our findings in spontaneous abortion. On the other hand, they do not extend any help in the problem of treatment—rather the reverse, considerably complicating any rational approach.

### Summary

The sera of 94 women were examined by a modified Rose-Waaler and the latex flocculation tests. Forty of the 94 were cases of spontaneous abortion, the rest were controls. Except for those women in the first trimester of pregnancy who subsequently aborted or threatened abortion, the Rose-Waaler and latex flocculation titers in the controls were within normal limits. In 29 of 30 cases of spontaneous abortion showing collagen lesions in the villi, the Rose-Waaler and latex flocculation titers were above normal limits. Five cases of abortion were due to other pathological conditions and for the remaining 5 no cause could be found.

Attention has been drawn to the parallelism between rheumatoid arthritis and spontaneous abortion.

A hypothesis has been advanced offering a partial explanation for the cause of spontaneous abortion covering the majority of cases.

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## URINARY EXCRETION OF PREGNANEDIOL AFTER INTRAVENOUS ADMINISTRATION OF PROGESTERONE IN THREATENED ABORTION

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THE relationship of the corpus luteum, progesterone, and pregnanediol, to endometrium and pregnancy<sup>1-4</sup> initiated much investigation. Crystallization of progesterone<sup>5-8</sup> and establishment of pregnanediol as an index of progesterone secretion<sup>9</sup> were two important results.

Progesterone is derived primarily from cholesterol,<sup>10</sup> and is secreted by the corpus luteum, adrenal cortex, and placenta.<sup>11, 12</sup> Ten to seventy milligrams per day is secreted during the luteal phase of the menstrual cycle,<sup>13</sup> and is represented by 2 to 7 mg. per day of urinary pregnanediol.<sup>14, 15</sup> Metabolism occurs primarily in the liver,<sup>3, 11, 16-23</sup> where progesterone is changed to pregnanediol, pregnenolone, and small amounts of lesser metabolites. These can be recovered from the urine, feces (bile), and expired carbon dioxide. Usually 10 to 20 per cent of administered progesterone is recovered as urinary pregnanediol<sup>24-28</sup>; however, when the intravenous route is used, only 5 to 6 per cent is found.<sup>29</sup> Tissue flooding of progesterone has been offered as an explanation for this.<sup>21</sup>

The physiologic effects of progesterone are well known.<sup>30</sup> A negative nitrogen balance<sup>13</sup> and somnolence<sup>31</sup> can be produced with large doses. During early pregnancy 50 to 400 mg. per day is secreted,<sup>13</sup> with a similar rise in the amount of urinary pregnanediol.<sup>32, 33</sup> This prompted administration of progesterone for threatened and habitual abortion, and has suggested the use of urinary pregnanediol determinations for diagnosis and as a guide for treatment of these patients.<sup>27, 34-38</sup> Guterman<sup>39</sup> and others<sup>13, 22, 41, 42</sup> have stated that in normally pregnant women 25 to 30 per cent of administered progesterone can be recovered as urinary pregnanediol, while only 10 to 15 per cent (nonpregnancy values) can be found in those who will have abortions. One hundred milligrams of progesterone daily was needed to increase fetal salvage.<sup>43, 44</sup> Some investigators<sup>44-46</sup> feel that factors other than endocrine are more important in abortion.

### Material and Method

Twenty-one patients of the Obstetric and Gynecologic Service of The Ohio State University Medical Center were used in this study. Fourteen of these had symptoms and findings consistent with a clinical diagnosis of

threatened abortion. Abortion was not threatening in 3 patients who were admitted for other reasons. All pregnant patients were between 2 and 4 months pregnant. Four patients were not pregnant.

Urine was collected with the use of an indwelling Foley catheter. A control collection of 12 hours was followed by the injection of progesterone, after which specimens were collected at 1, 2, 4, 8, 16, 24, and, if possible, 48 hours. The specimens were preserved with thymol and refrigerated until the pregnanediol determinations were performed.

Two hundred milligrams of progesterone prepared in propylene-glycol-albumin mixture<sup>47</sup> was administered intravenously. Vials of progesterone dissolved in propylene glycol (20 mg. per cubic centimeter) were kept on hand. Ten cubic centimeters of this solution was added to a fresh solution of 100 c.c. human serum albumin and 250 c.c. of 5 per cent dextrose in water immediately prior to administration. The progesterone solution was then given through blood transfusion tubing. All patients received the total infusion in 5 to 10 minutes. Following administration all patients showed some degree of somnolence, but could be readily aroused. All had a temperature elevation of 0.5 to 0.75 degree during the somnolent period. There were no complications from the procedure of administration.

Urinary pregnanediol was determined by the method of Sommerville, Gough, and Marrian,<sup>48</sup> which measures total pregnanediol as the free steroid. The technicians involved had had considerable experience with this method, which had previously been found to have "80 per cent or better" pregnanediol recoveries in this laboratory.<sup>29</sup>

TABLE I. INDIVIDUAL RESULTS. ABORTION WAS THREATENING IN CASES 8 THROUGH 21

CASE	WEEKS OF GESTATION	CONTROL (MG./24 HOURS)	% 24 HOURS	% 48 HOURS	OUTCOME
1	0	0.46	9.9	11.2	—
2	0	0.3	6.5	—	—
3	0	0.24	10.4	12.9	—
4	0	0.24	9.	9.6	—
5	11	5.3	6.97	—	} Normal pregnancies
6	13	4.8	4.8	5.5	
7	12	3.0	3.86	—	
8	14	12.36	9.15	8.9	} Delivered at or near term
9	12	11.36	5.9	6.2	
10	12	7.46	8.69	10.1	
11	12	3.9	7.32	17.02	
12	8	2.34	7.27	—	
13	16	9.4	3.84	4.04	} Aborted within four days
14	11	3.8	9.5	—	
15	13	2.8	1.5	0.71	
16	13	1.38	4.6	5.6	
17	10	0.14	4.9	4.5	
18	13	11.4	10.2	—	} Aborted after two weeks
19	11	9.6	3.86	—	
20	8	0.28	6.3	6.7	
21	8	0.18	11.2	—	

### Results and Comments

Because of the small number of patients in this series, only trends can be seen. The large variation in results of individual determinations also decreases the validity of the conclusions which can be made. These variations



are probably due to individual changes, often found when biologic and pathologic functions are dealt with. It is extremely doubtful that they are due to technique or inaccuracy, because this procedure has previously been performed in our laboratory many times by the same technicians (Table I).

Many of the following results agree with those of previous investigators. In several instances, however, diametrically opposed findings were obtained. In general the amount of pregnanediol recovered from progesterone was smaller than expected. This is also true for excretion during the control period, suggesting that most other methods include various other steroids in their final results.

Analysis of pregnanediol excretion (24 hours) prior to administration of progesterone (Fig. 1) shows that women who were not pregnant (4 patients) had an average excretion of 0.31 mg. per 24 hours with a range of 0.24 to 0.46 mg. Pregnant women without symptoms of abortion averaged 4.4 mg. per 24 hours with a range of 3.0 to 5.3 mg. These results were expected, although we thought the pregnant group would average nearer to 10 mg. per 24 hours. The difference in excretion between the pregnant and nonpregnant patient is undoubtedly accounted for by the increased circulating progesterone during pregnancy.

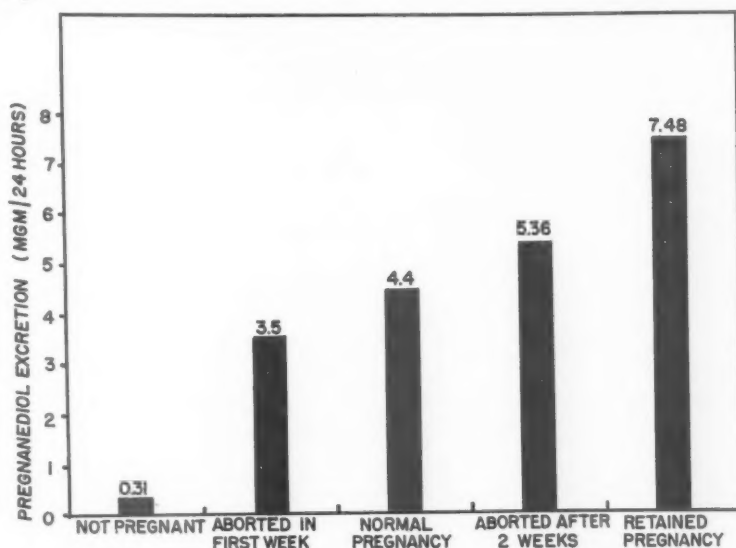


Fig. 1.—Pregnanediol (milligrams per 24 hours) before administration of progesterone. Those who had abortions later or retained their pregnancies showed more pregnanediol excretion. This could indicate stimulated secretion or conversion of progesterone.

Patients with threatened abortion (14 cases) were placed in three groups, depending on the clinical outcome of their pregnancy: those who retained their pregnancies (5 cases), those who had abortions two weeks or more after receiving progesterone (4 cases), and those who had abortions within one week (5 cases). Comparison of the controls for these with the controls for the normally pregnant group proves interesting. The average urinary excretion of pregnanediol in the group with early abortions (within one week) was 3.5 mg. per 24 hours. This is lower than the normal excretion and was expected. However, those who had abortions later or who retained their pregnancies excreted more (5.36 and 7.48 mg. per 24 hours, respectively). This is not entirely in agreement with data from other work, where low pregnanediol excretion was found in most of those who aborted. Several explanations for

this finding come to mind: (1) there is increased secretion of progesterone in an effort to maintain the pregnancy; (2) there is increased conversion of progesterone secondary to the stimulus of threatened abortion; and (3) perhaps a pathologic process cannot be compared to a physiologic one. In addition it is probable that the early abortions were actually inevitable instead of threatened, and represented dead products of conception and a return toward a nonpregnancy level of excretion.

If all cases of threatened abortion are divided into two groups representing more or less excretion than 5 mg. pregnanediol per 24 hours (as Guterman<sup>39</sup> proposed), one finds the following: (1) 50 per cent of patients who excreted more than 5 mg. per 24 hours aborted, and (2) 75 per cent of patients with less excretion aborted. This upholds to some degree the use of pregnanediol excretion as an indicator of abortion. A larger series of cases might make this more definite. It seems, however, that when patients are taken individually the ability to predict abortion or retention becomes almost worthless.

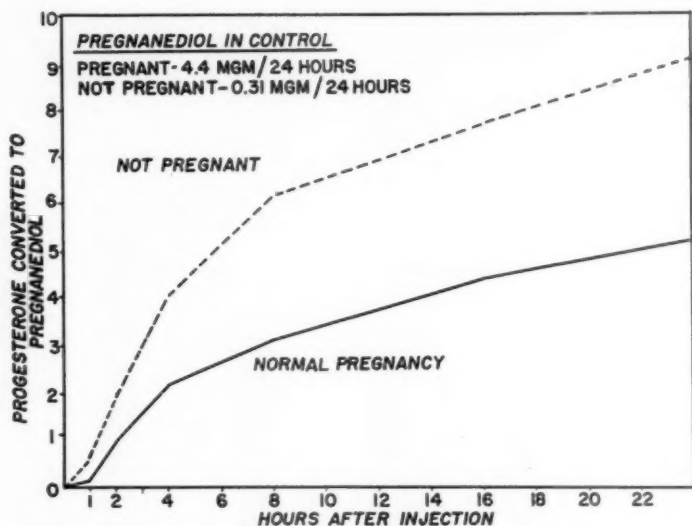


Fig. 2.—Per cent conversion in nonpregnant and normally pregnant patients. The increased conversion by nonpregnant women could be due to changes in the conversion mechanism during pregnancy.

When the per cent of progesterone converted to pregnanediol is plotted against time, the resulting curve is similar in all groups. There is a rather sharp rise during the first 8 hours and then a gradual leveling off. The percentages converted at 24 and 48 hours are usually similar, although in most instances the latter is slightly higher. This indicates that even though a large amount of progesterone is given rapidly, the excretion of pregnanediol from this injection extends beyond 48 hours. Is it stored somewhere and given up slowly, or is it diffused rapidly into the tissues and mobilized later? Individual excretion rates varied markedly. Average 24 hour conversion by groups was as follows: nonpregnancy, 8.9 per cent; normal pregnancy, 5.2 per cent; early abortion, 4.9 per cent; late abortion, 7.9 per cent; retained pregnancy, 9.1 per cent.

Comparing conversion for nonpregnant and normally pregnant women, we again get results different from those of other investigators. The pregnant patients converted about 5 per cent to pregnanediol by 24 hours, while the nonpregnant group converted about 9 per cent in the same time (Fig. 2).

Explanation of this fact is difficult, but seems to be associated with changes in the conversion system, storage of progesterone, or selective excretion of pregnanediol by the kidney. Of these the first two are the most likely.

Changes in the conversion system could be explained in several ways: (1) during pregnancy other metabolites could be produced from progesterone at the expense of pregnanediol; (2) during normal pregnancy there may be an optimum conversion controlled by the pregnancy or endocrine changes in pregnancy, so that only that progesterone needed is converted and used; (3) excess progesterone may be stored for use at some later date. This may be associated with (2).

As noted in Fig. 3, the higher the rate of conversion over that for normal pregnancy, the more likely the pregnant patient is to retain her pregnancy. Perhaps once abortion threatens, different factors come into operation and comparison with normal pregnancy is not valid. If this is so we can say that the higher the per cent conversion of progesterone to pregnanediol, the less

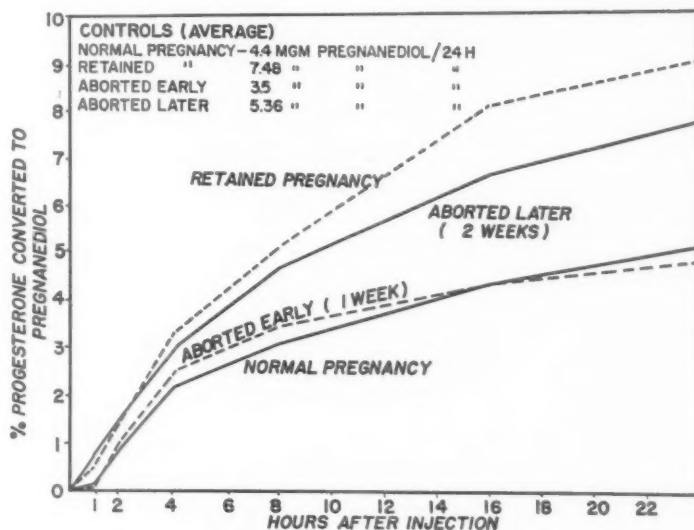


Fig. 3.—Per cent conversion during normal pregnancy and threatened abortion. When more progesterone is converted to pregnanediol, retention of the pregnancy is more likely to occur.

likely is abortion. It seems more plausible not to divorce normal pregnancy from threatened abortion. It appears that in normal pregnancy the conversion system is functioning at near optimum efficiency, so that unnecessary progesterone is not converted to pregnanediol. When abortion threatens, however, increased conversion or use (?) of progesterone is needed. The better the conversion system responds, the more likely retention of the pregnancy is to result. We can compare the progesterone conversion mechanism to a thermostat, and the force for changing the "setting" is the threat of abortion.

Therefore, possibly the inability to respond to progesterone rests in the conversion system, rather than on the amount of circulating hormone.

No consistent effect on the signs and symptoms of abortion followed the administration of progesterone.

### Summary

1. Twenty-one women were rapidly given 200 mg. of progesterone intravenously and the per cent of urinary pregnanediol recovered at various intervals

was recorded. Four of these patients were not pregnant and 17 were pregnant. Of the 17 pregnant patients, 13 exhibited symptoms and signs of threatened abortion at the time the drug was administered.

2. Urinary pregnanediol excretion in control specimens showed less excretion in the nonpregnant than in the pregnant women. However, women with threatened abortion who either retained the pregnancy or did not abort within two weeks of the determination had a higher average excretion than the woman with normal pregnancies.

3. About 9 per cent of the progesterone was converted to pregnanediol. The nonpregnant patients converted more than the pregnant ones. The more progesterone converted to pregnanediol, the less likely the patient was to abort. An explanation for these results is presented.

4. Conversion of progesterone to pregnanediol is still taking place in most instances 48 hours after injection.

5. Abortion occurred in 64.2 per cent of the patients with diagnoses of threatened abortion.

6. In our hands pregnanediol excretion and per cent of progesterone conversion are not useful tools for predicting abortion, or for determining which patients need progesterone therapy to prevent abortion.

7. Progesterone administration is probably of value in a small number of patients with threatened abortion, but should be used in doses of 100 mg. per day or more, and continued only if there is clinical improvement.

I wish to acknowledge the help and suggestions of Dr. Irving Rothchild, Cleveland, Ohio, in initiating this study.

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## TARNIER'S SIGN, AN AID IN THE DIAGNOSIS OF INEVITABLE ABORTION

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UTERINE bleeding during the first trimester of pregnancy often poses some perplexing problems for the attending doctor. An incomplete abortion can be diagnosed by the identification of expelled pregnancy tissue, and a curettage can be done if necessary. However, the differential diagnosis between a threatened and an inevitable abortion will occasionally require greater diagnostic acumen. We believe that one of the most helpful aids in this differentiation is the long known but seldom used Tarnier sign.

The Tarnier sign is defined as the effacement of the acute angle formed anteriorly between the neck and body of the pregnant uterus. This effacement indicates a contraction of the longitudinal fibers of the uterus, and hence a descent of the ovum itself, owing to dislocation from its site of attachment. A positive Tarnier sign indicates that the products of conception are at or within the internal os and that abortion is inevitable.

The value of the Tarnier sign as an aid in diagnosis is illustrated by the following case.

### Case Report

A 27-year-old para ii, gravida iii, was admitted to the hospital Jan. 24, 1956, with a history of progressively increasing vaginal bleeding over a 2 day period. Her last menstrual period was Oct. 25, 1955, and the estimated date of confinement was Aug. 2, 1956. The patient stated that she had soaked two Turkish towels with blood before coming to the hospital. Physical examination on admission showed her to be alert but quite pale. The blood pressure was 100/60, pulse 100. The red blood count was 3.1 million with 58 per cent hemoglobin. Rectal examination by the attending doctor disclosed what he thought was an inevitable or incomplete abortion. The bleeding continued and arrangements were made with the operating room for a dilatation and curettage. Because no pregnancy tissue had been identified as having been expelled, one of us was asked to examine the patient before curettage could be done.

Vaginal examination at this time revealed a uterus enlarged to the size of a 2½ to 3 months' gestation with a negative Tarnier sign, i.e., there was no obliteration of the acute angle formed anteriorly between the neck and body of the pregnant uterus. The diagnosis of incomplete or inevitable abortion was changed to threatened abortion and blood replacement was suggested, if necessary.

Conservative management followed. The bleeding stopped four days later and the patient was discharged in good condition on the seventh day. She subsequently was delivered uneventfully on July 30, 1956, of a 7 pound, 2 ounce, healthy male infant, just 6½ months after the episode of heavy bleeding.

### Comment

We believe that the Tarnier sign is a valuable diagnostic aid in differentiating the threatened abortion from the inevitable abortion. If no pregnancy tissue has been expelled, the presence of a closed cervix with a negative Tarnier sign should suggest further conservative management. Rectal examination, needless to say, is of no value in diagnosis of the source of bleeding during pregnancy. A vaginal examination must be done if accurate information is to be obtained. The amount of hemorrhage from a pregnant uterus is not a universally reliable criterion upon which to justify a curettage. It is our opinion that if the Tarnier sign is employed more widely as a diagnostic aid, an occasional viable pregnancy will continue to term that might possibly have been curetted under the erroneous diagnosis of incomplete or inevitable abortion.

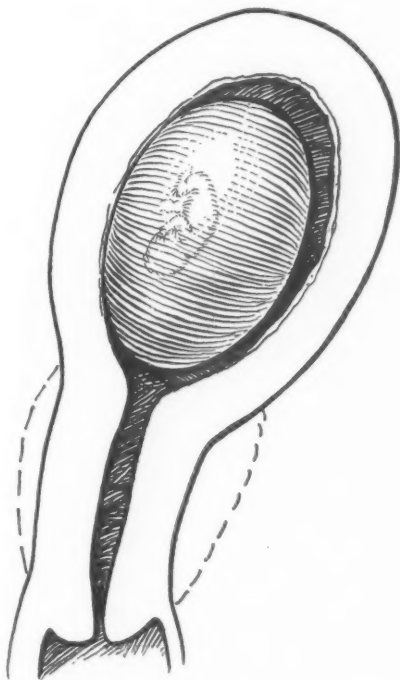


Fig. 1.—Negative Tarnier sign. Dotted lines represent positive Tarnier sign, i.e., the neck of the uterus has the shape of a pear (abortion has taken place).

A note about the originator of this sign may be of interest. Étienne Stéphane Tarnier is best remembered as the inventor of a very successful axis-traction forceps. He was the first to use a milk diet as prophylaxis in pre-eclampsia, and was also the first to use Listerism in obstetrics. He also designed one of the first incubators. He was born at Ayserey (Côte d'Or), France, April 26, 1828, and died in Paris on Nov. 24, 1897. He completed his medical studies in Paris where he taught and did most of his work. His description of the test<sup>1</sup> follows:

"There is still another peculiarity not mentioned by authors which appears of importance, inasmuch as it cuts off almost all hope of arresting the

progress of the symptoms. I allude to a particular form of the neck . . . . When contractions have lasted for a certain time, they have gradually dilated the internal orifice; the cavity of the neck has become confounded with that of the body and when the finger in the vagina is passed over the entire lower segment of the uterus, the neck can no longer be distinguished from it; a well defined limit between them is no more to be detected, and all that belongs to the neck of the womb has the shape of a pear, the larger part being continuous with the body of the organ, and the lower extremity corresponding with the external orifice. Whenever I have met with this condition of things, abortion has taken place."

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## SEPTIC ABORTION COMPLICATED BY SEROUS MENINGITIS\* †

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ALTHOUGH serous meningitis has been described and discussed in the neurological literature for many years, it has not, to our knowledge, appeared in the obstetrical literature. Its predilection for young women and the high abortion rate associated with it make it an entity of interest to the obstetrician-gynecologist as well as the neurologist and neurosurgeon. Also known as pseudotumor cerebri, pseudoabscess, and benign intracranial hypertension, the etiology of this condition remains obscure. The diagnosis depends on an increased cerebral spinal fluid pressure and symptoms secondary to increased pressure without any demonstrable lesion. Foley<sup>1</sup> reported in 9 women with this condition the following gestational results: 14 normal pregnancies, 2 stillbirths, and 8 abortions, or a fetal loss of 40 per cent. He postulated a hormonal or fluid imbalance as the cause. In the following case the condition coincided with hospitalization for a septic missed abortion.

A 28-year-old Negro woman was admitted to the Naval Hospital on Nov. 12, 1956, with the complaints of fever and a foul, bloody vaginal discharge. The last normal menses had been July 28. She had noted slight breast soreness and nausea in August and a 10 day episode of spotting in early September. On September seventeenth she experienced what she described as a sudden gush of "bloody water." She was seen in the outpatient clinic on September 28 when the uterus was noted to be approximately the size of an 8 weeks' gestation. The cervix was closed and no discharge was seen. Because of her history she was advised to return every two weeks for examination. On November 12 she noted a foul, bloody vaginal discharge which required four pads during the day. She presented herself at the hospital and was admitted.

The patient was a gravida vi, para iv, who had had one abortion. The past history was noncontributory except for a previous admission at this hospital in May, 1956, when a missed abortion was evacuated by curettage.

Physical examination on admission was negative except for a uterus enlarged to the size of a 6 weeks' gestation, a temperature of 101° F. and a foul, bloody uterine discharge. The adnexa were negative. The patient did not complain of headache or visual disturbances and a careful neurological examination was not done at this time. Urinalysis was negative. A leukocytosis of 22,800 was present, with neutrophils 82, lymphocytes 12, and band forms 6. The hemoglobin was 12.2 Gm., erythrocytes 3.88 million and the hematocrit 35. From her previous admission she was known to have a sickle-cell trait, but no sickling was noted on smears. The patient denied any instrumentation or interference. A diagnosis of infected missed abortion was made and she was started on penicillin and

\*Presented at a meeting of the Obstetrical Society of Philadelphia, Jan. 3, 1957.

†This article is not to be construed as necessarily reflecting the views of the Department of the Navy.

streptomycin. On the third hospital day she was still febrile and the odor of the discharge still strong. Anaerobic cultures were negative for *Clostridium welchii* organisms but *E. coli* had grown out of the aerobic cultures. A scout film of the pelvis was negative for foreign body. On pelvic examination the cervix was found to be open and a 1 by 1 by 4 cm. mass of putrid placental tissue was removed from the cervical canal. The patient complained of a frontal headache for which she was given aspirin and codeine with some relief. Her temperature continued to be 101-102° F.

On November 15, with continued complaints of frontal headache, a neurological examination was made, and bilateral papilledema, lateral nystagmus to the right, and a stiff neck were noted. Neurological consultation confirmed these findings. A spinal tap revealed 330 mm. pressure and slightly cloudy fluid. The cell count was 300 lymphocytes. No polymorphonuclear leukocytes were found. An angiogram was negative for a frontal lobe lesion. A tentative diagnosis of right cerebellar abscess was made and intravenous Terramycin therapy begun.

On November 16 a burr hole was made in the right occipital bone and by means of a ventricular tap decompression was carried out. The posterior fossa was exposed with the posterior lip of the foramen magnum ronguered away. The dura was noted to be under pressure. Cerebellar explorations demonstrated no abscess on either right or left. The dura was opened in the midline and the arachnoid punctured. A gush of fluid under pressure was obtained. The wound was closed. The fluid obtained had the same cellular characteristics as the spinal tap on the previous day. Cultures were negative except for *Micrococcus pyogenes* which was felt to be a contaminant.

The patient made an uneventful recovery. The uterine discharge and the headache disappeared and she became afebrile. The papilledema disappeared by the eighth post-operative day and she was discharged to be followed in the outpatient clinic.

On December 13, the patient was seen in the clinic. She was asymptomatic, pelvic examination showed normal findings, and the eye grounds were normal. On December 20 she experienced a normal menstrual period.

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## PATIENT REACTION TO PUERPERAL SURGICAL STERILIZATION\*

### I. General Considerations

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SINCE the proposal of early puerperal tubal ligation by Skajaa<sup>1</sup> in 1932 and the introduction of the operation into this country by Adair and Brown,<sup>2</sup> surgical sterilization of the female has increased in its frequency. There have been a considerable number of studies of the procedure reported in the past years—with respect to its legality,<sup>3, 4</sup> its bacteriology,<sup>5</sup> its failure rate,<sup>6, 7, 8</sup> and its mortality rate.<sup>7, 8, 9</sup> The present papers, however, are concerned with the psychosexual and socioeconomic aspects of the operation. The need for such a study is perfectly evident; all surgical procedures which impinge on the reproductive tract occupy a peculiar place in the life and adjustment of the patient, and this is particularly true when sterilization results. A consideration of the failure rate represents a natural and human concern on the part of the surgeon, but ignores the fate of the "successful cases." It is well for the obstetrician-gynecologist to recognize the impact on the total emotional life of his patient and of her family of the operation he performs.

It is difficult to assess the medical effect of the introduction of early puerperal sterilization. Certainly it has reduced the incidence of cesarean section performed largely for delivery and simultaneous sterilization<sup>10</sup>; it has likewise reduced the patient's total hospitalization by combining the convalescence from delivery with the convalescence from a "minor operation." It has probably increased the acceptance of the procedure, since many women who agreed with the advisability of such a procedure would consent to postpartum tubal ligation but would not agree to a more major procedure such as hysterectomy or even interval bilateral resection of the cornua. The fact that tubal ligation was introduced into this country on the threshold of the age of the sulfonamides and antibiotics, however, renders morbidity and mortality comparisons<sup>9</sup> difficult to evaluate. Certainly there seems to be a tendency to enter the abdomen for the exclusive purpose of interrupting tubal continuity more freely in the 1950's than in the early 1930's.<sup>6, 10</sup> The restraining influence has shifted from the threat of possible medical complications to a concern for the validity of the indications.<sup>8, 11-14</sup>

\*Aided by a grant from National Academy of Sciences, National Research Council.

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Despite this apparent rising frequency of surgical sterilization,<sup>15</sup> studies of the psychological impact of the procedure are conspicuously lacking. Most of the postoperative follow-up surveys are based on written questionnaires rather than on personal interviews designed to determine the over-all impact on the woman of the knowledge that she is permanently sterilized.

The legality of surgical procedures carried out for the purpose of sterilization is surprisingly difficult to determine. Holman<sup>16</sup> in 1954 cited only Connecticut, Kansas, and Utah as prohibiting such a procedure except for instances of medical necessity. On the other hand, a survey\* in late 1956 which was responded to by every one of the 48 states seems to indicate prohibitions against it in eleven states, and no one of the states mentioned by Holman appears on this list. Any surgeon performing such a procedure should be accurately informed as to the laws of his own state, and in general is best advised, legally, to confine the operation to patients who present medical indications.

In MacDonald House the policy is expressly stated that surgical sterilization can be carried out only "for medical indications." This leaves unanswered the question, "When does parity, per se, constitute a medical indication?" On this question there is little unanimity of opinion, and every definition of a degree of parity which justifies granting the request of the patient for tubal ligation is a definition which is bound to be challenged. With the rising morbidity and mortality of grand multiparity,<sup>17</sup> there appears to be little reason for forcing the woman to achieve this precarious status before granting her request for surgical sterilization. During the period covered by this study, it was held that "a gravida iv or more of 32 years of age or more, who had a demonstrated failure of nonsurgical techniques of contraception, was entitled to bilateral partial salpingectomy if she and her husband so desired." It was also held that three cesarean sections constituted a medical indication for sterilization if desired by the patient and her husband. Whether or not the "medical indication" represented organic illness, or the definition of parity cited above, signed consultation between two members of the Staff (one of whom could be the patient's physician) was required in all cases. Considering these various standards, it should be noted that the expression "a demonstrated failure of nonsurgical techniques of contraception" quickly became meaningless, since this history would be presented with varying degrees of reliability by all patients anxious for the operation.

### Plan of the Study

The records of 457 women who had had puerperal bilateral partial salpingectomy in this institution between Jan. 1, 1952, and May 1, 1955, were taken for study. This figure represents 3.27 per cent of the total of 13,945 deliveries performed during this 41 month period. A trained social worker with considerable experience in personal interviewing and in counseling women was engaged to contact these patients individually. The interviewing was carried

\*Survey conducted by the Cleveland Health Museum, personal communication from Dr. Wynfield Doyle. Either the State Attorney General or the Department of Health of each state responded. The states listed in this survey as prohibiting sterilizations are: Arkansas, Florida, Kentucky, Louisiana, Missouri, New Jersey, New Mexico, Pennsylvania, Rhode Island, Texas, and Wyoming.

out in the patients' homes; husbands were interviewed where this was considered necessary, and the case worker traveled over 2,000 miles to carry out the study. The survey was conducted during the late months of 1955 and the first half of 1956, and the average length of time from the operative procedure to the date of interview was 2½ years, while the range was from 6 to 48 months.

Of the 457 operations performed, 169 were on private patients (2.02 per cent of the 8,343 private deliveries during this time) and 288 on Staff patients (5.14 per cent of the 5,603 Staff deliveries). Of these 457 women, a total of 311 (68 per cent) were interviewed for this study. The composition of the group interviewed indicates that about 54 per cent of the private patients who had been operated upon and 76 per cent of the Staff patients operated upon were contacted. The reasons for noninterview are indicated in Table I.

TABLE I. REASONS FOR NONINTERVIEW OF THE 146 PATIENTS WHO WERE NOT CONTACTED FOR THIS STUDY

	PRIVATE	STAFF
Not interviewed because of religion (Catholic)	35	0
Private physician did not want patient interviewed (known to be non-Catholic)	14	0
Moved out of city	13	9
Whereabouts unknown	8	33
Non-Catholic patients who did not wish to be interviewed	4	0
Located but appointments could not be arranged	3	20
In State Hospital with psychosis (dating from preoperative period)	1	1
Died since operation (death not related to operation)	0	5
Total	78	68
		146

Since the categories of patients not interviewed has, by a process of selection, an influence on the composition of the study group, it is well to consider the various reasons for noninterview cited in Table I. In refusing to be interviewed, the Catholic patients tended to express evidences of guilt and in some instances bitterness. Interestingly, the guilt reaction was expressed in a few instances by the physician (Protestant) who had performed the operation on a Catholic patient. None of the Catholic physicians on the staff had performed bilateral partial salpingectomy; the corresponding hysterectomies performed by Catholic physicians after multiple cesarean sections for "a diseased uterus" are not included in this study. The private physicians who requested that their patients not be interviewed were concerned about the medical-legal aspects of having revealed the contents of the medical record to the interviewer (actually, the case worker was made a member of the Department of Social Service of the University Hospitals, giving her the same proper access to records which any social service department has). It is difficult to evaluate the true reasons for noncooperation of this small group. The women who were located but with whom appointments could not be arranged were mainly women who worked. After many extensive telephone contacts with these patients, the case worker became convinced that this represented a bonafide difficulty and was not an excuse to cover guilt reactions or regret over the procedure. In each instance the 5 patients who had died had succumbed to the organic illness which was the indication for the sterilization in the first place.

What the elimination of these groups of patients does to the composition of the study group is problematical. Of the women who were geographically available yet who were not interviewed (i.e., all except those not located and those who had moved or died), it is probably safe to assume that the majority had some degree of negative reaction to the procedure.

At each interview some 40 different questions were asked of each woman. These covered a wide range including financial status, marriage adjustment, personal fears, and emotional reactions, as well as physical health. Many of the questions overlapped so that the same information was elicited under different guises. None of the questions was asked in a routine questionnaire manner, and the worker devised many techniques for rechecking the validity of answers by rephrasing various items. Most of the interviews assumed a free and easy, informal air, and the answers were not recorded in the presence of the patient. In many instances a rapport was established which led to far more personal information being volunteered than was solicited. The worst person to have carried out these interviews would have been a physician, and it was felt that a woman with training but the ability to disguise this training represented the best means for obtaining the desired reaction. At the conclusion of each interview the case worker graded the interview candidly from the point of view of patient cooperation and probable honesty. For both private and Staff patients the ratings in this respect were quite similar: 58 per cent were considered Very Good both in setting and rapport established; 30 per cent were rated as Good; and only 12 per cent Fair to Poor.

### Results

A brief consideration of Table II and of the multiplicity of factors evaluated in the interviews, as well as of the range of patients, indicated that no simplified interpretation of the information obtained is possible. The present consideration is chiefly concerned with the composition of the group studied, the principal indication for the operation, together with the superficial response of the patient to her current status.

TABLE II. DISTRIBUTION OF PATIENTS INTERVIEWED BY AGE, PARITY, RACE, SOCIOLOGIC BACKGROUND, AND RELIGIOUS AFFILIATION

	PRIVATE	STAFF
Age, average	33.4	31.5
Parity, average	4.2	6.6
Living children at time of interview	3.5	5.6
White	86	14
Negro	5	206
Income, average	\$9,800	\$3,600
Living conditions*		
A	88½%	25%
B	10½%	45%
C	1%	30%
Religious affiliation		
Protestant		
Husband	85%	92%
Wife	88%	93%
Catholic		
Husband	3%	8%
Wife	2%	7%
Jewish		
Husband	12%	—
Wife	10%	—

\*A, families living alone in a respectable area or better; B, those living alone in slum areas; C, those in crowded conditions in slum areas.

Table II summarizes some of the pertinent factors concerning the general picture of the patient group. The distinction between the Staff patients and the private patients in this group of women who had surgical sterilization is



approximately the same as the differences between all Staff and all private patients in MacDonald House. In general, there is less difference between the Staff and private patient groups in age, parity, numbers of living children, and religious preference than is seen in their socioeconomic background. Interestingly enough, the racial distribution percentagewise, as well as the age and parity, of the noninterviewed (as determined from their medical record) agreed with these same factors among the interviewed.

In considering the indications for the operation, two sources were used, the patient's statement and the medical record. In general, these two agreed fairly well, although there was noted a tendency of the patient whose indication was actually multiparity to cite as the indication her dwindling health, whereas not infrequently the woman with organic illness, to whom this had been minimized by her medical attendants, would cite the number of children. Broadly speaking, the indications for sterilization in these women can be divided into three groups: the organic medical, the previous cesarean sections, and "multiparity." There were 66 women whose principal indication was medical, 65 who were sterilized because of repeated cesarean sections, and the remaining 180 because of their multiparity.

There are, of course, many varied reactions to sterilization, ranging from a feeling of personal guilt to aggression against the surgeon, from a sense of being defeminized to a sense of relief. The present summary, however, is concerned only with the most superficial of these reactions, namely, whether or not the patient in retrospect "liked" the operation and her subsequent reproductive status. From the point of view of evaluating this single response to the operative procedure, information from two sections of the interview was available: that asking if the patient would have the operation repeated, and that asking if the patient regretted the change in her reproductive status. Strictly considered, these two questions do not encompass identical ground, since many women regret the finality of the procedure the minute it is over, but still, recalling their condition at the time of operation, might vote for its repetition.

TABLE III. ANSWERS TO THE QUESTION AS TO WHETHER OR NOT THE WOMAN WOULD HAVE THE OPERATION PERFORMED AGAIN UNDER THE SAME CIRCUMSTANCES (EXPRESSED AS PER CENT OF THE TOTAL GROUP)

	PRIVATE	STAFF
Yes (without qualification)	56	68
Yes (some degree of qualification)	34	23
No (despite preoperative unanimity between husband and wife)	6	4
No (with a record of preoperative reluctance on the part of one of the partners)	4	5

TABLE IV. PERCENTAGES OF THE TOTAL GROUP WHO EXPRESSED REGRET OVER HAVING BEEN SURGICALLY STERILIZED, CONSIDERED BY ORIGINAL INDICATION FOR THE OPERATION

	NUMBER	% NO REGRET	% AMBIVALENT.	% REGRET
Organic illness	66	67	30	3
Cesarean section	65	67	19.5	13.5
Parity	180	92.2	6.1	1.7

For the total group the percentages of patients who would repeat the operation are indicated in Table III. This shows that for both the private and Staff groups roughly 10 per cent, if given another opportunity, would not have the operation performed. It does not indicate, however, the original indication for surgery in this dissatisfied group. Table IV indicates those expressing



either regret, no regret, or some degree of ambivalence with respect to the primary indication for the tubal ligation. In general it can be seen from this that those who had the procedure performed for multiparity were the most pleased. The reasons most frequently cited were the improvement in the economic situation, with a greater ability to plan for the future, together with the factors of more time and strength to invest in the family they already had, and the elimination of the constant fear of pregnancy.

The high percentage of ambivalent response by those who had organic illness as their chief indication revolved in most instances around a genuine desire for more children coupled with a regretful recognition that their physical condition did not permit additional pregnancies. In most instances, however, these patients had been perfectly aware of the symptoms of their organic illness and could recall the strain of pregnancy. In sharp contrast, the 20 per cent of women in the cesarean section group who gave ambivalent answers had experienced no symptoms of illness. Their concern had been instilled by their physicians, with warnings of possible uterine rupture, but their most frequent phrase was that they "had been told," rather than that they could remember.

The outstanding figure in Table IV, however, is the nearly 14 per cent of cesarean section patients who unequivocally regretted having permitted the tubal resection. In general, these women expressed the feeling that they had been "talked into" the sterilization procedure. This, combined with the fact that 7 per cent of the babies born at the time of the tubal ligation had subsequently died, accounted for the sharp dissatisfaction with the operation performed for the indication of cesarean section scars. In other words, of the total number who expressed definite regret over having had the procedure carried out, 57 per cent were in the cesarean section group, although this was the principal indication in only 21 per cent of the total group.

The question as to whether or not these women were actually "talked into" the operation can be approached in another way. Table V indicated the numbers and percentages of the interviewed patients who expressed regret, no regret, or ambivalence on this score, correlated against the answer to the question as to who first suggested that the procedure be carried out. In evaluating the answers to this question there were, of course, two sources of information: what the patient said at the time of interview and what the hospital record indicated. Interestingly enough, these two sources agreed in 90 per cent of the cases; in the remaining 10 per cent in which there was some disparity, the evidence of the record was accepted, without significantly altering the final statistics.

TABLE V. PERCENTAGES OF THE TOTAL GROUP WHO EXPRESSED REGRET OVER HAVING BEEN SURGICALLY STERILIZED, CONSIDERED FROM THE POINT OF VIEW OF ORIGIN OF THE SUGGESTION

SUGGESTED BY	NUMBER	% NO REGRET	% AMBIVALENT	% REGRET
Physician	186	69	27	5
Patient	125	91	6.5	2.5

In 60 per cent of our cases the first suggestion for sterilization came from the physician, and it can be seen from a consideration of the figures in Table V that, if the procedure was originally proposed by him, there was twice the chance that the ultimate patient reaction would be one of regret and four times the chance that there would be an ambivalent response on this topic. On the contrary, if the patient initiated the suggestion, there was over a 90 per cent chance that the ultimate patient evaluation would be one of "no regret."

### Summary

The present paper initiates a survey of the psychosexual-sociologic reaction of the surgically sterilized woman. The survey was carried out by individual interview conducted in the patient's home by a woman trained in social work and experienced in marriage counseling. The present report deals chiefly with the composition of the patient group studied and the superficial reaction to the procedure expressed in terms of having "regretted" or "not regretted" the loss of the ability to bear children.

In general, the women who were persuaded to undergo the procedure by the physician expressed more regret than did those who themselves requested the operation. Over 90 per cent of the patients who suggested the procedure themselves expressed no subsequent regret. Also, the patients whose primary indication for sterilization was organic disease or previous cesarean section indicated more regret than did those whose principal indication was a high degree of parity. Sixty-four per cent of the women who expressed subsequent regret over being sterilized had had multiple cesarean sections as the principal indication for the procedure. While no final conclusions can be reached from this particular study, it appears that the women who themselves suggest bilateral partial salpingectomy on the basis of their high parity are the women who in retrospect are the least likely to experience regret over the procedure.

We find it difficult to express adequately our very great obligation to Mrs. Ruth Erinstein who conducted the interviews. Her grasp of the objectives involved was instantaneous, her impartiality awe inspiring, and her effort dogged. Without her we might have started, but without her we could never have finished.

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## SOME PSYCHOSOMATIC ASPECTS OF OBSTETRICS AND GYNECOLOGY\*

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THE term psychosomatic began to appear in the English literature about twenty-five years ago, but was not used frequently in the general medical literature until the past decade. One might inquire if we have developed, and are to discuss this evening, a new concept of disease. In 1860, Sir James Paget,<sup>1</sup> a leading pathologist and surgeon, wrote: "The cases are so frequent in which deep anxiety, deferred hope and disappointments are quickly followed by the growth or increased growth of cancer that one can hardly doubt that mental depression is a weighty addition to other influences that favor the development of the cancerous constitution."

I submit that Sir James Paget was thinking in psychosomatic terms even though, in 1860, he had never heard the phrase. Numerous quotations are available from the writings of Benjamin Rush, Austin Flint, Palmer Howard, Herbert Snow, and others to indicate that leading clinicians of the nineteenth century were able to discuss the causes of disease in terms which we would now regard as somatic and psychosomatic without any awareness that the two were incompatible. What happened to our concept of disease in the early years of this century?

It is probable that the germ theory influenced medical thought strongly.<sup>2</sup> In the early years of this century, investigators and clinicians devoted themselves to determining the cause of a disease. The physical sciences made remarkable contributions to medical progress and focused our attention upon organ and cellular pathology. Research became synonymous with the laboratory, a situation well expressed by William James<sup>3</sup> when he wrote: "Many persons nowadays seem to think that any conclusions must be very scientific if the arguments in favor of it are all derived from the twitching of frog legs—especially if the frogs are decapitated—and that, on the other hand, any doctrine vouched for chiefly by the feelings of human beings—with heads on their shoulders—must be benighted and superstitious."

Within the sphere of medical education, our leading teachers derived visible pleasure from demonstrating to students the manner by which multiple symptoms and disseminated disease could be reduced to a single cause. Such a case was and unfortunately may continue to be known as "a good case." The

\*Presented at a meeting of the Brooklyn Gynecological Society, April 17, 1957.

ideal of a clean-cut diagnosis and the complete cure was held before students and graduates who were then sent into the very different world of medical practice.

In the past decade changes have occurred rapidly. There has been recorded a growing dissatisfaction with medical education, a dissatisfaction which has been expressed by clinicians, medical educators, and the general public.

There appears to be an increased awareness on the part of clinicians that in many cases of human suffering no single cause exists and that in other cases patients do not get well even though the cause has been removed. In the field of medical education one finds recurring references to the need for a broader concept of human biology. Also, in these past ten years the contributions of modern biochemistry and physiology have suggested functional pathways between the emotions and altered metabolism while the contributions of dynamic psychiatry have made less mystic the development of the human personality. Thus there has evolved, I believe, a medical climate more favorable to the re-growth of psychosomatic concepts.

These then are the introductory points which I would like to present for your consideration—that the psychosomatic concept is not new, but that it was almost lost under the avalanche of early contributions from the physical sciences; that the more recent contributions of the physical sciences and of psychoanalysis have suggested interrelationships between the psyche and the soma and at the same time have suggested methods by which these relationships can be studied more critically; that in some instances the skilled clinical interview may be as important an investigative method as is chemical titration.

### Definition of Term Psychosomatic

It might be helpful to define at this point what is meant by psychosomatic. By this I refer merely to an orientation that attempts to understand health and disease as the total reaction of multiple biologic processes including those of the personality. It is apparent that all phases of living, including those phases called health and disease, contain elements that are psychological and somatic. It is apparent also that a fine line of division cannot be drawn between what is exclusively psychological and what is exclusively somatic. Nevertheless, one cannot help but be impressed by the importance of the psychosomatic interaction in some clinical situations. It must be remembered, however, that the relative importance of this interaction may vary in different patients within the same disease entity. If the foregoing sounds complex, I would reply that biologic phenomena are complex. Fortunately, biologic phenomena are also orderly and permit the formulation of general principles which may then be used to collect and to communicate specific knowledge.

An important contribution of modern psychiatry is to have shown that the general principles of stress and adaptation, which apply to the equilibrium of the body chemistry, apply also to the equilibrium of the total individual in his society.<sup>4</sup> Using this biologic frame of reference, let us examine first the nature of the psychological stress of pregnancy; second, some common adaptive devices which women employ to maintain psychological stability during pregnancy; and, third, some factors which may determine the magnitude of the stress and the success of the adaptive devices.



### Psychological Stress of Pregnancy

For the most part, our knowledge is derived from the psychoanalytic study of pregnant women by competent analysts. This knowledge explains and at the same time may be confirmed by obstetrical observations which most of us have made.

In a psychosomatic sense, pregnancy is a threat to every woman.<sup>5</sup> There may be some physicians who would reject this statement as inconsistent with clinical experience. We have all known healthy women who were sincerely overjoyed with their pregnancies. But if we think more deeply, it is apparent that at a physical level the pregnancy is an endoparasite that depends completely for its survival upon the maternal reserves. If these reserves have been lowered by disease, the pregnancy may be an actual physical threat to the health of the woman. Even in physically normal women, the somatic reserve is seldom such as to enable the woman to experience pregnancy in a symptom-free state. At a psychological level, pregnancy changes a woman's life by placing her more in the role of a giver. Temporarily or permanently, she must give up her physical comfort, her figure, and possible social or intellectual goals, and assume increased responsibility not only for nine months but for many years. The sacrifices required and the increased social-biologic responsibilities of pregnancy are much greater for the woman than for the male. Any event which so changes a person's life constitutes a threat or stress to their previous equilibrium. Hence, what has been observed psychoanalytically appears to fit with biologic reasoning.

The psychological adaptive devices used by reasonably healthy women to meet the stress of pregnancy vary with the period of gestation. Perhaps the most common adaptive device used by reasonably healthy women to meet initially the stress of pregnancy is identification. In psychoanalytic terms the pregnancy is absorbed into the woman's own ego. Stated another way, the woman perceives the pregnancy emotionally as an integral part of herself. To her, "The pregnancy is myself." Early in pregnancy this is an effective adaptive device because what is perceived and accepted as an integral part of oneself is not as threatening as what is perceived as a foreign body. With this identification between patient and pregnancy there is a turning inward of her interests. This identification between patient and pregnancy, this turning inward of the interest, has many clinical manifestations.

Consider the terms used by women early in pregnancy. Invariably they refer to the situation as "my pregnancy." In regard to behavior, consider the young wife who has enjoyed going out evenings, often to the dismay of her husband. Upon learning that she is pregnant she is apt to lose interest in these activities and prefers to stay at home, to read, to knit—even though it may appear on critical examination that she is not quite sure what she is knitting. She prefers to feather the nest, if you will. Her interests have turned inward. Consider the older woman who is a leader in various local committees. Upon learning of her pregnancy, she is apt to lose interest in these outgoing activities. She may still go—but she goes not to plan social events so much as to talk about "my pregnancy," often to the utter distraction of her nonpregnant friends.

Finally, consider the so-called normal symptoms of pregnancy. For the most part they are symptoms related to body functions of which the patient is daily and repetitively aware. I do not mean that these symptoms are psychogenic. I do mean that the inversion of her interests may cause the patient



to be more aware of the symptoms and at times to discuss them with a type of enjoyment. Her interests have turned inward as a result of the psychological identification that has occurred between her and the pregnancy.

Yet, if this emotional union between patient and pregnancy were to persist, birth would represent a psychological amputation. However, the reasonably healthy woman comes gradually to feel that her pregnancy is not really herself but instead is a separate object with a potential of its own. There are physical determinants for this emotional shift. At about the eighteenth week she begins to feel fetal movements. The physician announces that he hears the fetal heartbeat. These events, aided perhaps by hormone or other chemical changes, serve to help her to surrender the identification from which she unknowingly derived such gratification. At about this time we note the emergence of another psychological adaptive device—phantasy.

There is psychoanalytic evidence that in mid-pregnancy women derive considerable emotional gratification from their phantasies about the baby and that this gratification is another adaptive device which enables them to adjust psychologically to the continuing stress of pregnancy. Again, psychoanalytic observation explains and at the same time is confirmed by obstetric observations.

Not that patients divulge their phantasies directly; they are quite secretive about them. But in most instances it is at this time of gestation that the patient begins to exhibit indecision as to whether to knit a pink bonnet or a blue bonnet, regardless of how many bonnets she may already have knitted. It is at about this time that we are asked whether it is to be a boy or a girl. The patient may know we cannot answer—I have even heard pregnant obstetricians ask the question. They protect themselves intellectually by making a joke of the question—but still they ask. The pregnancy has been accorded a separate identity and the patient is deriving emotional satisfaction from phantasizing about the child. Finally, consider the average patient who is allowed to listen to the fetal heartbeat or who, at this stage of pregnancy, is told something about the development of the baby. Even patients who have heard fetal heartbeats and who know intellectually the information being given them, show an interest and gratitude of a degree that is difficult to explain except for the fact that what they hear helps them to phantasize; helps them to adopt this adaptive device.

As term nears, even formerly complacent women may appear to become somewhat anxious. Careful evaluation will show that in most instances this anxiety is merely an eagerness to get "it over with." At the same time observation will disclose changes in the woman's interest and attitude that contrast with those observed earlier in pregnancy. Near-term patients chafe at maternity clothes, even though they are now more comfortable in such clothes; they are impatient at the restrictions of a term abdomen.

The phantasies have begun to pall and no longer are an adequate source of ego gratification. The woman's interests begin to turn outward again and she is now eager to get "it over with" because she is eager to have the baby as a real rather than as an imaginary object. This then is the final psychological adaptive device, aided in its development by physical factors, which helps in the preparation of the normal woman for the trials of labor and for the assumption of maternal responsibility in the puerperium.

The puerperium is another difficult period of adjustment. The woman is now faced with the baby—the living, undeniable proof of her sexuality and of her current and future responsibilities. For a few women this is too much. They deny the reality of the situation by becoming psychotic. When this occurs, there can be no doubt that the birth acts only as a trigger

mechanism to precipitate clinical illness in women who have been ill for years, even though their previous defenses were such as to have prevented recognition of their illness. It might be said that birth does not cause postpartum psychosis so much as it destroys previous defenses which the woman had erected. Even in psychologically healthy women the stress of the puerperium is apt to lower the psychological reserve. Thus, we are all familiar with the frequent occurrence of mild and transient postpartum depressions in otherwise stable women.

The magnitude of the psychological stress and the success of the adaptive devices depend, chiefly, upon the circumstances of the woman's past life and depend, to a lesser extent, upon the circumstances of her current life situation. In the course of her psychosexual development, the motherly woman has accepted her biologic endowment and has developed a harmonious interplay between a desire to be loved at a heterosexual level and a desire to give—to give of herself even to the extent of accepting pain and other sacrifices in order to give. The development of this harmonious interplay depends upon many factors but study indicates that the woman's own mother and her childhood relationship to her mother is of central importance. However, only the purely masochistic woman enjoys pain and sacrifices as ends in themselves. The reasonably well-adjusted woman retains the need to receive—to feel loved and to feel secure while she is giving of herself to a pregnancy and a newborn infant. Thus, to a lesser but still important extent, the circumstances of her current life may affect the magnitude of the stress. If the woman feels secure in her husband's love and her doctor's interest, her previously determined ability to give may enable her to adjust to the stress of pregnancy along lines we have described. If her early life experiences were such as to make the giving that is required by pregnancy unusually threatening or if she feels insecure in her current life environment, difficulties may arise.

### Doctor-Patient Relationships in Pregnancy

In discussing what we can and cannot do with this knowledge in the practice of obstetrics, we cannot emphasize too strongly that the cornerstone of an effective psychotherapeutic approach is the doctor-patient relationship and the manner in which this relationship is utilized by the physician. Most women exhibit the need for a dependent type of doctor-patient relationship during pregnancy. The degree of dependency varies with the woman's own inner security but to some extent dependent needs are manifested by all pregnant women. At a physical level she needs to feel that she can depend upon the obstetrician's technical competence. Usually the very fact that she has exercised a free choice in selecting the physician indicates that she has commenced the relationship feeling satisfied at this level of dependency—his technical competence. All that is subsequently necessary is the manifestation of a confident attitude by the physician during the course of pregnancy and labor. Consequently, this aspect of the relationship is seldom a problem. At a psychological level the woman needs initially to feel secure in the obstetrician's personal interest in her as an individual and, later in pregnancy, to feel secure in his interest in both her and the unborn child. In most instances these psychological needs can be fulfilled merely by listening to the patient talk about herself early in pregnancy and about herself and the baby later in pregnancy. During labor, the dependent psychosomatic needs are further fulfilled through periodic visits and encouragement by the obstetrician early as well as late in labor. The foregoing may sound obvious

but thoughtlessness on our part or the demands of an excessive practice may at times prevent the fulfillment of these normal psychological requirements.

It is often inadequate, however, to create a doctor-patient relationship that attempts only to fulfill dependent psychosomatic needs. Indeed, if this is all that is attempted, some women may become so dependent as to make excessive or unreasonable demands from which they gain no benefit. Consequently, the second and more difficult objective is to utilize the doctor-patient relationship so as to increase the woman's acceptance of her biologic endowment and to help her acquire a realistic confidence in her own ability to fulfill this endowment. To state this in another way, we should attempt to gain her confidence not as an end in itself; instead, we should try to use her confidence in us to increase her confidence in herself. In this objective we are limited. We cannot alter a patient's basic personality or deal directly with deep-seated conflicts during the course of prenatal care. This requires the special skills of the trained psychiatrist, and the science of psychiatry, like the science of obstetrics, has its limitations. Nevertheless, we can do a great deal in many instances by utilizing the proper doctor-patient relationship to deal more effectively with physical and psychological facts or situations that are current, conscious, and realistic. Specific illustrations are almost as numerous as patients, but to list a few common examples, we can:

1. Emphasize by our attitude the normalcy of the patient and of the biologic situation. It is doubtful that this is accomplished effectively when normal patients are routinely given unnecessary medications or placed routinely on arbitrary restrictions during pregnancy. At the same time it must be recognized that an occasional woman may be so dependent as to require the psychological benefit that will be derived from medications and restrictions that are not apt to do physical harm. The wise physician will attempt to recognize these differences in patients.

2. Recognize and attempt to protect psychological adaptive devices that best serve the needs of the individual patient. For example, the phantasy of mid-pregnancy is a healthy adaptive device. We should attempt to encourage it by such devices as allowing this patient to listen to the fetal heart and discussing fetal growth and development.

3. Manipulate the individual environment so as to lessen realistic physical and psychological stress. Included in this are attempts to promote the display of interest and affection by the husband during the pregnancy and puerperium.

4. Provide factual instruction, the importance of which has long been accepted. It now appears, however, that this biologic instruction may have special psychological value if it is given personally by the physician rather than obtained by reading. The recent tendency toward the establishment of prenatal group instruction conducted by responsible personnel may have added value as a form of superficial group psychotherapy.

In the study of gross pathology, a generation of doctors have noted that prevention is preferable to cure and that cure is more likely if treatment is based upon early recognition. Lund<sup>6</sup> has related the importance of this to obstetrics when he pointed out that after a female child has been discharged by her pediatrician her next prolonged medical contact is apt to be with an obstetrician.

To this might be added the observation that pregnancy is a period of psychosomatic stress which tends to reveal previously hidden areas of lowered psychological reserve. Consequently, I believe the psychosomatic approach



may have its greatest value in the obstetric phase of our specialty and for this reason have devoted most of my time this evening to a discussion of the psychosomatic aspects of pregnancy.

### Psychological Stress of Hysterectomy

Most of us are quite aware that psychological factors may influence the development and course of gynecologic disease or symptoms. Indeed, most of the psychosomatic literature in our specialty relates to gynecology. One cannot help being perplexed by the scope of this literature, by the many uncritical observations that have been published, and by the tendency of some authors to interchange personal opinion with established fact. It may be of interest to review some points of female psychosexual development which are established fact, and to attempt to focus this knowledge upon a practical gynecologic problem, the psychological preparation of a patient for hysterectomy.

In discussing this problem we are concerned with the psychological meaning of the menstrual and reproductive functions and must understand the range of psychological stress associated with the loss of these functions. We must also comprehend in at least a general way the psychological interaction between gynecologist and patient and from the foregoing formulate practical principles for the psychological preparation of the individual patient.

It is well established that the biologic *ability* to reproduce is intimately connected with the adjustment of the woman as a feminine figure. I stress the word *ability* because many well-adjusted women do not reproduce owing to circumstances beyond their control. In such cases, normal maternal drives may be sublimated successfully through a career, adoption, or other devices. Nevertheless, the *ability* to reproduce is a cornerstone of the woman's psychosexual adjustment. If we go back further to examine the adolescent years we find that the female child is conditioned by fact and hearsay to equilibrate the menstrual function with her ability to reproduce. Depending upon her preadolescent life experiences and intrapersonal relationships, this equilibration between menses and reproduction may provoke anxieties which she may or may not resolve in her progress toward maturity. If her anxieties are unresolved she is apt to erect defenses against them and these defenses may prove troublesome to her for the rest of her life. Regardless of the individual reaction, the adolescent girl does associate intimately the menstrual and reproductive functions. As it has so often been said, menstruation is the badge of femininity. Consequently, not only the *ability* to reproduce but also its outward manifestation, the menses, are cornerstones of psychosexual adjustment. Thus, even in women who are sterile, the menses may be of psychological importance.

Our studies<sup>4</sup> lead us to believe that the loss of the menstrual function is perceived by the woman as a blow to normal feminine self-esteem. We also believe that in most women the degree of this trauma can be anticipated and lessened by appropriate medical management.

In the case of the relatively mature woman, the medical history will contain data which indicate that the patient has accepted and utilized her feminine role to acquire and to maintain warm intrapersonal relationships. While there are exceptions within this so-called mature group, it is obvious that the trauma of hysterectomy will tend to be greater in the younger woman and in the woman who has not yet established a satisfactory marriage and family. It is also apparent that hysterectomy will have little or no psychological trauma for postmenopausal women who have already adjusted to the loss of the menstrual and reproductive functions. However, and this is not apparent except by close study, the climacteric is a period when

old doubts and insecurities may emerge. Consequently, the climacteric is another age when hysterectomy may cause an increased psychological stress for relatively stable women.

### Doctor-Patient Relationships in Gynecology

In the case of the relatively mature woman the psychological management depends upon the gynecologist's awareness of these normal reactions. He understands and is sympathetic to the psychological stress in the case of the climacteric or sterile woman, just as he understands the stress of the younger, fertile patient. Hysterectomy is not advised abruptly but is introduced as a procedure to be considered and its indications are discussed. When possible, the patient's attention is directed to the fact that conception is unlikely or impossible because of the pelvic disease and not because of the proposed operation. Her attention is directed gently to the fact that, if untreated, the disease state is or may become harmful to her as an individual, as a wife, or as a mother. Her positive achievements—marriage, children, a career—are thereby emphasized. If it is thought that ovarian function can and should be preserved, the importance of this function is explained. Such a discussion may have two psychological values for the relatively mature woman. First, it helps convince her that the physician is not a cold technician who unfeelingly and autocratically deprives her of a valued organ and function. This commences a doctor-patient relationship which may be used later for further therapeutic purposes. Second, the discussion may commence an emotional shift in which the patient comes to view the uterus with its reproductive and menstrual functions not as a prized possession but as the site of an abnormality which is or may become detrimental to her as an individual and as a woman. However, this emotional shift takes time. Because of this and because hysterectomy is seldom an emergency procedure, absolute plans for the operation often are not made at the time of the first consultation. Instead, the patient is reinterviewed on one or two subsequent visits. Patients who in this way are allowed time to work through normal anxieties preoperatively will experience less troublesome reactions postoperatively. At the time of operation, an informed husband may be of great psychotherapeutic value. He should be cheerful, attentive, and affectionate during the postoperative period. Gifts and behavior which indicate the wife's value to him—in appropriate cases, feminine negligees, the visits by children or the encouragement of the early use of cosmetics and hairdressers—are of inestimable value and contrast with the psychologically blunted policies of (1) no hospital visits by young children and (2) no coitus for six weeks. In mentioning the latter I do not mean that intercourse should be advised prematurely. I do mean to call attention to the fact that many uninformed husbands may find this instruction difficult and as a defense against their own drives may avoid the display of any affection or desire, thus tending to confirm the inner fears of many wives.

The grossly neurotic woman presents different problems. She suffers from a lifelong disturbance in psychosexual development. Often she is beset by strong conflicts between accepting and rejecting the feminine role. She attempts unconsciously to solve her conflicts and anxieties by means of various defenses. Because her basic difficulties are unknown to her, she cannot tell us about them directly. However, the physician who has learned to listen and to observe may often recognize these patients by the defenses which they exhibit. These defenses include masculine behavior, exaggerated erotic behavior, frustrated maternal attitudes, and numerous somatic symptoms which are without adequate organic reason. Not infrequently such patients describe their physical symptoms with exaggerated adjectives while they are observed



to sit comfortably during the interview and even to display a type of satisfaction for being such a diagnostic dilemma. Study<sup>7</sup> indicates that some neurotically ill women may unconsciously seek suffering—including surgery—as punishment for irrational guilt and are apt to exhibit a dramatic sense of well-being after an operation. Patients of this type are likely to be looked upon as exhibiting a good postoperative result. At a time when most patients are complaining of postoperative pain they are proclaiming how fine they feel. An honest follow-up over a period of months may be necessary to reveal that such relief is almost always transient.

Because the gynecologist cannot learn the exact nature of the deep-seated difficulties in the individual woman who is neurotically ill, it is difficult to determine which patients may exhibit an adverse reaction following hysterectomy. For this reason it is wise to avoid operation in such patients unless it is based on strong indications. When operation cannot be avoided safely, our experience leads us to believe that the defenses exhibited by the neurotic woman may provide a rough clue as to her postoperative reaction. We believe we have observed adverse emotional reactions more frequently in women who display seductive and provocative behavior or who exhibit frustrated maternal attitudes preoperatively.

In the psychological management of the neurotically ill woman with organic pelvic disease, we believe that the doctor-patient relationship is again of crucial importance. The gynecologist displays an attitude that is kind but authoritative and strict. To a degree that seems reasonable he listens to the emotional problems about which the patient is able to talk, but he does not ask probing questions nor does he become involved directly in an attempt to treat her psychological problems. He provides medical attention to the extent that is indicated by the pelvic disease and avoids well-meant but ill-advised promises as to the result of surgery. He avoids repetitious, unnecessary pelvic examinations and is alert for signs of mental depression or neurotic outbursts during the pre- or postoperative period. If it seems indicated, the temporary aid of a psychiatrist may be enlisted preoperatively and postoperatively. When it is thought that such help would be refused by the patient we find that it often can be provided under the guise of a medical consultation. At the time of operation, well-considered psychiatric factors may occasionally influence the choice of operative procedure. I have occasionally done just a myomectomy simply to preserve the menstrual function in a neurotically ill woman in whom further reproduction was unlikely. The use of the vaginal approach and the avoidance of an abdominal scar may have some preventive value in the excessively narcissistic woman.

### Summation

In closing, I would like to summarize our opinions as to the psychological knowledge that the ideally trained obstetrician-gynecologist should possess and what he can hope to do with this knowledge in his practice. These opinions are shared by the Departments of Obstetrics-Gynecology and Psychiatry at the University of Rochester and represent eight years of observation. During these eight years, six of our Chief Residents have voluntarily requested and received a year of clinical training in psychiatry before they assumed their responsibilities as Chief Resident in Obstetrics-Gynecology. This has provided the two Departments with a teaching experience the results of which have been published.<sup>8</sup>

We believe the ideally trained obstetrician-gynecologist should be familiar with existing knowledge as to the psychology of acute and chronic disease, of pregnancy and sterility, of menstruation and the menopause, and with the emotional significance of pelvic examinations and pelvic surgery. Because the psychological content of the foregoing varies greatly in different women, we believe he should possess the skill in medical interviewing that is necessary to accumulate data by which his knowledge may be applied to an individual patient. Last, we believe he should possess a conscious understanding of the various relationships that may be established between patient and doctor and the manner by which a particular relationship may be utilized to the benefit of a particular patient.

The obstetrician-gynecologist is in an enviable and strategic position to use psychosomatic knowledge first, to recognize early those patients who are marginally adjusted and, when feasible, to refer them to a psychiatrist for evaluation as to treatment; second, to recognize psychological adaptive devices that best serve the needs of an individual patient; third, to encourage and protect useful psychological adaptive devices by dealing directly with physical and psychological factors that are current, conscious, and realistic. Attempts to uncover and to deal directly with unconscious conflicts are incompatible with the practice of obstetrics-gynecology.

Last, we have observed that an increased understanding of human behavior results in a more mature recognition of medical limitations, with the result that the clinician is made less anxious by his inability to cure every symptom and is therefore less likely to become disturbed in his relationship toward certain types of patients. He may be less likely to manipulate facts to fit traditional concepts or to employ, as a manifestation of his own anxiety, major surgical procedures to deal with physical symptoms that he may suspect are emotional but which he does not know how to cure.

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## Gynecology

### EFFECTS OF THREE 19-NOR STEROIDS ON HUMAN OVULATION AND MENSTRUATION\*

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REPORTS of the influence of oral progesterone and of three synthetic progestins, 17 $\alpha$ -ethinyl-19-nortestosterone (I),<sup>†</sup> 17 $\alpha$ -ethinyl-5(10)-estraneolone (II), and 17 $\alpha$ -ethyl-19-nortestosterone (III),<sup>‡</sup> on indices of human ovulation have already been made.<sup>1, 2, 3</sup> Herewith are more details from the study of 40 unreplicative patients receiving various dosages of the first two compounds, as well as of 10 other patients who were treated with the third. By the Clauberg test, this is a very potent progestin in rabbits.<sup>4, 5</sup> The effects of these three synthetic steroids are discussed in relation to menstruation, ovulation, and fertility.

#### Material and Methods

##### *Selection of Patients for Treatment.—*

With one exception, the 50 women treated were patients of the Reproductive Study Center, or of the Fertility and Endocrine Clinic, at the Free Hospital for Women. Detailed study of these cases had failed to disclose definitive cause for childlessness. The women were chosen in the hope, born of previous encouraging experiences from treatment of similar patients with progesterone alone<sup>1</sup> or in combination with diethylstilbestrol,<sup>6</sup> that the anabolic synthetic steroids to be used would have a beneficial effect on the musculature and, therefore, on subsequent function of uteri and oviducts.

\*This study was aided by grants from the Planned Parenthood Federation of America, Inc., and G. D. Searle & Co. The compounds used were contributed by G. D. Searle & Co. and the Chemical Specialties Co., Inc.

<sup>†</sup>For convenience, the numbers I, II, and III are used in the text and tables to denote these respective steroids. Compound I was formerly manufactured by Chemical Specialties Co., Inc. Compounds II and III are manufactured by G. D. Searle & Co.

<sup>‡</sup>Nilevar, trademarked product of G. D. Searle & Co.

By selection, our group was essentially homogeneous. Age distribution is presented in Fig. 1; quality of infertility and duration of exposure are shown in Fig. 2. The ages ranged from 22 to 39 years (mean, 29.5; median, 29.4; mode, 29.2). Exposure covered 2 to 10 years except in 8 instances: 4 patients were habitual aborters; 3 had secondary infertility; and one primarily infertile woman had been exposed to conception for not more than 1½ years.

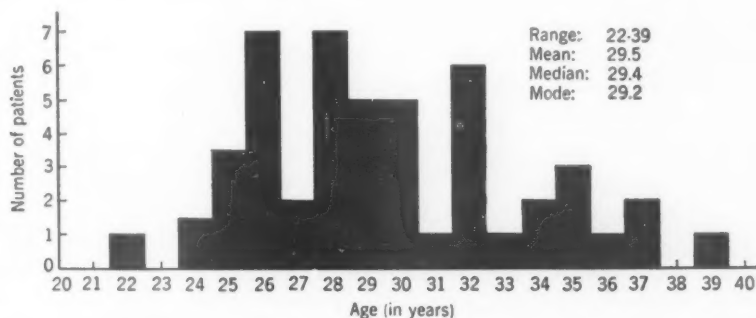


Fig. 1.—Age distribution of 50 women treated orally with synthetic progestins. (From Rock, Garcia, and Pincus.<sup>3</sup>)

Figs. 1-6 reproduced by permission from Academic Press Inc.

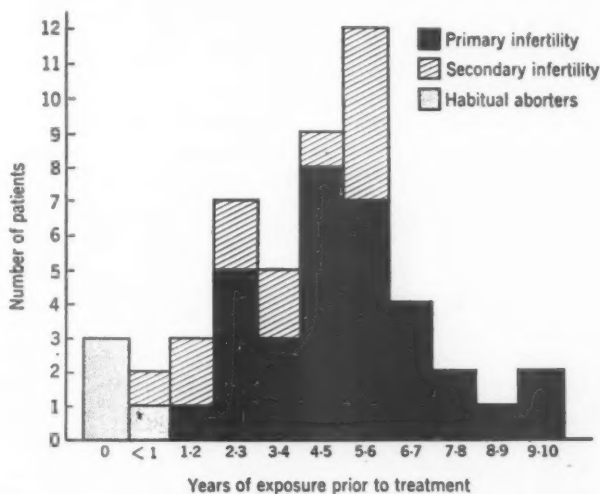


Fig. 2.—Quality and duration of infertility in 50 women prior to oral treatment with synthetic progestins. (From Rock, Garcia, and Pincus.<sup>3</sup>)

Elsewhere<sup>3</sup> have been discussed certain characteristics of normal menstruation.

In 1939, Rock, Bartlett, and Matson<sup>7</sup> studied the menses of 392 women in the Fertility and Endocrine Clinic of the Free Hospital for Women. They concluded that women, in cycle after cycle, show by endometrial biopsy a positive relationship between premenstrual ovulation and the regularity and similarity of recurring menstrual periods. Previously (1937) Rock and Bartlett<sup>8</sup> had reported that, with few exceptions, a biopsy indicating progesterone effect was followed by menstruation at intervals roughly commensurate with the degree of progestational development. It was noted, conversely, that when the biopsies revealed only proliferative changes, succeeding catamenia usually varied



widely in quality, quantity, and duration of flow, and failed to occur in any recognizable temporal relationship to the cycle day of a biopsy and to the extent of endometrial proliferation without secretion (Fig. 11 of Rock and Bartlett<sup>8</sup> and Figs. 1, 2, 3 of Rock, Bartlett, and Matson<sup>7</sup>).

Since in the nonpregnant normal female effective amounts of a progestin have never been shown to be derived from any other source than the corpus luteum, and an early corpus luteum invariably has the stigma of rupture, we believe it can be assumed that women whose several successive catamenia are similar ovulate before most, if not all, menses. Similarity of catamenia, then, is one of our criteria of the normal menstrual cycle, for it is taken to indicate recurrent ovulation.

In our experience, practically all women who, for many months, repeatedly flow similarly in quality, quantity, and duration, have menses which follow each other within a limited time range characteristic of each individual. The exceptions are those comparatively few who have true oligo- or polymenorrhea. For the majority of patients, the group range lies between about 24 and 36 days and, in such women, the length of successive cycles varies within the narrower limits of about 5 days. We require, then, for normal menstrual cycles not only similarity of flow, but also regularity, within a range of 5 days; and these 5, within the outer limits of 24 and 36 days.

In order to keep the experimental group as uniform as possible, selection was limited, with but few exceptions, to patients who habitually menstruated in this way.

#### *Procedure.—*

The methods of study have already been described.<sup>1, 2, 3</sup> Briefly, these women were observed during (a) a control menstrual cycle when no medication was given; and (b) one or more cycles in which a synthetic progestin was administered orally in dosages ranging from 5 to 50 mg. per day, usually from day 5 through day 25 of the cycle\*; and, finally (c), during one to 3 post-medication cycles.

In both control and experimental cycles, careful notice was taken of the length of the cycle, of the quality and duration of flow, and of any interval bleeding. To obtain all possible information on occurrence of ovulation, daily basal body temperatures were recorded, daily vaginal smears were examined, endometrial biopsies were taken within cycle days 19 and 24, and the urinary output of pregnanediol was ascertained within cycle days 17 and 23. Excretion values for 17-ketosteroids were determined in order to detect any possible influence of these progestins on adrenocortical secretion. Finally, as a check on the completeness of each 48 hour collection of urine, the creatinine content was measured.†

The vaginal smears were stained by the method of Shorr<sup>9</sup> for the diagnosis of ovulation time.

Endometrial examination was based on criteria proposed by Rock and Bartlett<sup>8</sup> in 1937, and slightly modified by Noyes, Hertig, and Rock<sup>10</sup> in 1950.

The pregnanediol was determined by the method described by Rogers and McLellan<sup>11</sup> with the modification that the "pregnanediol" complex from the aluminum oxide column is subjected to a Girard reaction to remove ketonic chromagen, the nonketonic fraction being reacted with sulfuric acid for the

\*In a very few exceptional cases where the lengths of the cycles were longer, medication was given on different schedules, according to the particular lengths of cycles.

†It should be pointed out that unfortunately it was not possible to perform every test in every cycle. However, at least two criteria of ovulation were available in each control and experimental cycle.



characteristic color reaction. By this procedure in a number of experiments, sodium pregnanediol glucuronide added to urine has yielded pregnanediol averaging 92 per cent of the amount added.

The 17-ketosteroid content was ascertained by the Zimmermann color reaction of the neutral ketone fraction, after Pincus.<sup>12</sup>

Creatinine determinations were carried out according to the method of Folin, as described in *Practical Physiological Chemistry* by Hawk and associates.<sup>13</sup>

In order to check even more accurately the effects of these steroids on ovulation, as manifested by changes in the ovaries and endometrium, required laparotomies in 7 patients not in the regular series were performed during or just after one to 3 cycles of medication. Ovaries were carefully examined in the gross in all these instances and, in 5, ovarian biopsies were taken for microscopic study. Correlation with the endometrium was also possible in 5 of the cases.

In 28 patients of the regular series, menstrual and ovulatory data were studied during one or more cycles subsequent to therapy. Also, during the posttreatment cycles, 38 of the women were questioned as to any untoward effects of therapy. Fertility records were kept for the entire group of 50 patients.

### Immediate Effects of Therapy

In Table I the findings in 50 control cycles and 125 cycles of steroid medication in 50 women are arranged according to the dosages of the compounds administered.

#### *Compounds I and II.—*

These are discussed together because, except on the 5 mg. per day level, the 2 compounds had almost identical effects.

*A. Control Cycles.*—In view of this, as well as of the homogeneity of the subjects, both in respect to their pertinent characteristics previously described, and to the similar results of premedication tests, it was decided, for control purposes, to regard the 40 subjects receiving I and II as a single group. Hence their values are averaged.

The mean length of the 40 control cycles was  $27.2 \pm 0.51$  days.

Whether or not ovulation occurred was deduced from results of at least 2 tests, and often of 3; i.e., from basal body temperatures, endometrial biopsies, and vaginal smears. The data for each of these indices were classified as positive (+), indicating ovulation, doubtful ( $\pm$ ), when findings were equivocal, and negative (-). Doubtful and negative group percentages for each test are listed in Table I. The sum of the doubtful ( $\pm$ ) and negative (-) percentages deducted from 100 would then constitute the positive values.

In the 39 control cycles for which temperature charts were furnished, ovulation was recorded as doubtful ( $\pm$ ) in 6 per cent, and negative (-) in 6 per cent; hence in the rest (88 per cent), ovulation tests were positive. Since, of the 37 endometrial biopsies, none is recorded as either doubtful or negative, 100 per cent were positive. Of the 31 vaginal smears studied in the control cycles, none was negative (-), only one (3 per cent) was doubtful ( $\pm$ ); i.e., 97 per cent were positive. At the cycle time tested, the mean 24 hour output of pregnanediol in 35 normal untreated menstrual cycles was  $3.4 \pm 0.27$  mg., and of 17-ketosteroids in 32 cycles,  $5.2 \pm 0.47$  mg. The mean creatinine content in 31 control cycles was  $1.21 \pm 0.039$  Gm. per day, indicating that the urine collections submitted for analyses were complete.

*B. Treated Cycles.*—Some patients received only 5 mg. per day of compound I or II, but as this dose was found to give variable results, we postpone discussion, of these cases.

TABLE I. EFFECTS OF 17 $\alpha$ -ETHINYL-19-NORTESTOSTERONE (I), 17 $\alpha$ -ETHINYL-5(10)-ESTRAENOLONE (II), AND 17 $\alpha$ -ETHYL-19-NORTESTOSTERONE (III) UPON LENGTHS OF CYCLES, INDICES OF OVULATION, AND STEROID AND CREATININE OUTPUT IN NORMALLY OVULATING WOMEN

COM- POUND	DOSAGE (MG./ DAY)	MEAN LENGTH OF CYCLE (DAYS)	INDICES OF OVULATION																PREGNANE- DIOL (MG./DAY)		17-KETO- STERIODS (MG./DAY)		CREATININE (GM./DAY)	
			BASAL TEMP.			ENDOMETRIAL BIOPSY			VAGINAL SMEAR			PREGNANE- DIOL (MG./DAY)		17-KETO- STERIODS (MG./DAY)		CREATININE (GM./DAY)								
			NO.	%±	%-	NO.	%±	%-	NO.	%±	%-							NO.	%±	NO.	%±	NO.	%±	NO.
Control*	-	27.2 ± 0.51	39	6	6	37	0	0	31	3	0	35	3.4±	0.27	32	5.2±	0.47	31	1.21±	0.039				
I	5	40.4 ± 5.26	9	0	100	9	0	100	9	11	89	9	0.27±	0.068	9	5.6±	0.82	8	1.26±	0.054				
I	10	28.9 ± 5.56	20	5	95	21	14	86	20	25	75	20	0.24±	0.037	20	5.4±	0.73	18	1.24±	0.087				
I	20	28.6 ± 0.57	36	3	89	25	20	76	35	17	83	32	0.35±	0.073	29	4.4±	0.45	29	1.33±	0.047				
I	40	26.8 ± 1.16	5	0	100	4	50	25	4	0	100	3	0.97±	0.97	1	8.7		1	1.02					
I†	10-40	28.5 ± 0.68	61	3	92	50	20	76	59	19	81	55	0.34±	0.066	50	4.8±	0.40	48	1.29±	0.044				
II	5	21.0 ± 2.41	4	0	75	3	0	67	4	0	75	3	0.23±	0.100	3	4.7±	1.34	3	1.24±	0.047				
II	10	26.5 ± 0.58	28	14	79	22	0	96	26	19	65	26	0.25±	0.052	26	4.1±	0.35	25	1.17±	0.083				
II	20	27.7 ± 0.26	6	0	100	6	0	83	6	0	100	6	0.53±	0.335	6	6.3±	1.96	6	1.28±	0.101				
II†	10-20	26.7 ± 0.48	34	12	82	28	0	93	32	16	72	32	0.30±	0.074	32	4.5±	0.47	31	1.19±	0.069				
Control	-	25.7 ± 0.91	9	10	0	11	0	0	8	0	0	10	3.1±	0.23	10	6.7±	0.86	10	1.33±	0.122				
III	10-50	25.3 ± 2.24	13	0	100	11	0	91	10	0	100	10	0.31±	0.038	10	8.7±	2.49	10	1.41±	0.043				

\*The 40 subjects who received compounds I and II are regarded as a single group, hence their control values are averaged, for these compounds had almost identical effects.

†The test values for each dosage of over 5 mg. in treated cycles are averaged, since these women were sufficiently alike in pertinent respects.

Since results at 10, 20, and 40 mg. per day of compound I were similar, these values are averaged and discussed as a unit. Table I shows there was no significant change in the mean cycle length of the 62 cycles during which 10 to 40 mg. per day was administered, in comparison with the control mean ( $28.5 \pm 0.68$  vs.  $27.2 \pm 0.51$  days). However, the incidence of ovulation, as deduced from the 3 tests, differed markedly from the values prior to treatment. A large and significant increase in the percentage of negative (-) diagnoses, compared to those in the controls, occurred in every test, and in the case of the endometrial biopsies and vaginal smears, an increase, as well, in the percentage of doubtful ( $\pm$ ) specimens.\* Furthermore, by the more direct criterion of ovulation, i.e., pregnanediol excretion, a notable decline in output of this end product of progesterone metabolism (from  $3.4 \pm 0.27$  to  $0.34 \pm 0.066$  mg. per day) clearly indicated an inhibition of ovulation, thus confirming the deductions from the 3 indirect tests. Indeed, in a number of instances, no pregnanediol whatsoever could be detected. In only one cycle, that of a patient receiving 40 mg. per day of compound I, was an excretion value within the normal range obtained. The data, therefore, strongly suggest that corpus luteum activity (if, indeed, there was a corpus luteum present at all), was considerably reduced or even abolished by the medication.

In contrast, the 17-ketosteroid output was diminished only slightly and not to a statistically significant extent; i.e., from  $5.2 \pm 0.47$  to  $4.8 \pm 0.40$  mg. per day, a decline of only 4 to 15 per cent, as compared to 72 to 94 per cent decrease in pregnanediol. This suggests that the pituitary gonadotropin which evokes progesterone (the precursor of pregnanediol) was greatly inhibited, whereas the tropic factor concerned with 17-ketosteroid precursor production, presumably adrenocorticotropin, was not suppressed to any significant degree.

The constancy of the creatinine output lends validity to the urinary assays.

Examination of the data from 5 mg. per day dosages of compound I discloses entirely similar results to those obtained with higher dosages in terms of ovulation indices, pregnanediol, 17-ketosteroid, and creatinine output. Only at the lower dosage, however, was there a significant increase in mean length of the cycle in 4 cycles of 4 women. This prolongation was accompanied by minor vaginal spotting occurring some time between cycle days 14 and 25 with no bleeding following withdrawal of the medication. The vaginal staining was not typical of menstrual bleeding. Though a "break-through," it more closely resembled withdrawal flow, for it varied in quality, quantity, and duration. On the other hand, 5 cycles (2 subjects) studied at this low dosage were of normal length and showed no abnormal bleeding or staining.

As has been stated, the results with compound II, except for those in 4 patients who received 5 mg. daily, were quite similar to those obtained with I. These 4 patients, 3 of whom also stained during medication, had a significant shortening of the cycle from a mean of  $27.2 \pm 0.51$  (the premedication value of 40 control cycles) to  $21.0 \pm 2.41$  days. On the other hand, in the patients who received daily dosages of 10 or 20 mg. per day of compound II, there was (1) neither "break-through" bleeding nor a significant change in mean length of the cycle; (2) on the basis of at least 2 of 3 indices, suppression of ovulation was indicated; (3) the mean pregnanediol output for this 10 to 20 mg. per day group was markedly and significantly reduced (from a premedication value of  $3.4 \pm 0.27$  to  $0.30 \pm 0.074$  mg. per day); and (4) there was a slight and nonsignificant decline in the mean 17-ketosteroid excretion.

### C. Comparison of Effects of Compounds I and II.—

1. *Statistical group comparison:* As noted above, the effects of I and II, except at the 5 mg. per day level, were practically identical. Thus, the

\*The endometrial effects of medication will be discussed later.

TABLE II. EFFECT OF COMPOUND I ON OVARIES AND ENDOMETRIUM (OPERATIVE SERIES)

PATIENT NO.	DOSE (MG./DAY)	NO. OF TREATED CYCLES	DURATION OF THERAPY	DAY OF CYCLE AT OPERATION	OVARIES				ENDOMETRIUM	
					CORPUS LUTEUM		FOLLICLES		GLANDS	STROMA
					GROSS	MICROSCOPIC	GROSS	MICROSCOPIC		
1	10	1	Days 5-25	Day 6	0	—	+	—	Atypical proliferative	Predecidua
				(Next cycle)						
2	20	1	Days 5-23	Day 24	Very old (Corpus albicans)		0	Possibly scant primordial	Atypical proliferative	Predecidua
3	10	1	Days 5-25	Day 27	0	0	1 follicle	Developing follicle	—	—
4	10	1	Days 5-23	Day 24	0	—	0	—	Atypical proliferative	Predecidua
5	10	3	Days 5-25	Day 5	0	0	0	Possibly scant primordial; some cystic follicles	—	—
				(First following untreated cycle)						
6	10	1	Days 5-20	Day 21	Old	Old	0	Possibly scant primordial	Atypical proliferative	Predecidua
7	10	2	Days 16-25 Days 5-22	Day 23 (Second cycle)	Old	Old	Few regressing follicles barely visible	Cystic and atretic follicles	Secretory exhaustion	Predecidua



variations in the data on lengths of cycles, indices of ovulation, steroid and creatinine output would not serve to differentiate one compound from the other. This was so for either of these compounds whether at a dosage of 10, 20, or, in the case of I, of 40 mg. per day.

The variations in percentage of equivocal ( $\pm$ ) and of negative ( $-$ ) values for the ovulation indices have been compared statistically by the chi-square test, and these have been found to differ significantly ( $\chi^2 = 27.95$ ,  $P = 0.001$ ). The major contribution to  $\chi^2$  is made by the frequency values for "doubtful" ( $\pm$ ) endometrial diagnoses. Therefore, compounds I and II, in dosages of 10 mg. per day and above, exert identical effects on the basal body temperatures and vaginal smears but, by this statistical method, II appears to be somewhat more effective in suppressing the characteristic secretory pattern of the endometrium.

*2. Intragroup variations:* Although the mean values for cycle lengths may show no significant differences between control and experimental cycles or between the 2 types of compounds tested, significant individual variations may be masked. Thus, one subject receiving 10 mg. per day of compound I had a 63 day cycle. (This patient did in fact have some vaginal spotting on cycle days 21 to 26, and may therefore have manifested the type of effect described above for the 4 patients who received 5 mg. per day of compound I.) None of the patients who received II at any dosage used exhibited this prolongation of cycle. Theoretically I and II should serve to sustain the endometrium during therapy and should yield withdrawal flow after cessation of treatment. Thus, in 2 instances, I was taken beyond day 25, i.e., to day 30; and bleeding occurred on the thirty-second and thirty-third days, respectively. Similarly, in one case, I was taken to day 37, whereupon the patient began to flow on day 38.

On the basis of the statistics shown in Table I, the mean latent period from cessation of treatment to menstrual bleeding was 3.5 days (for 10 to 40 mg. per day of I) and 1.7 days (for 10 to 20 mg. per day of II).

The frequency of atypical break-through menstruation-like flow at 10 mg. per day and above was as follows: for I, 5 out of 62 cycles; and for II, 3 out of 34 cycles. The earliest onset of flow during treatment was on day 20 in a patient who, in her control cycle, had menstruated on day 22. Thus, the type of "uncatamenia-like" break-through bleeding prior to day 20 which we had observed in a significant proportion of patients receiving oral progesterone<sup>1</sup> occurred but rarely in subjects taking 10 mg. per day or more of either I or II.

#### *D. Effects on Ovulation of Compounds I and II.—*

*1. Conclusions based on criteria of ovulation:* As generally conceded, it may be difficult or impossible to recognize true ovulation in a normal cycle by any single index. This may be due to atypia or inaccurate recording of basal body temperature, a biopsy specimen which is inadequate or taken at the wrong time in the cycle, or faulty vaginal smears. It is therefore of interest to evaluate our results on the basis of more than one diagnostic observation.

Referring only to indirect criteria, the data are conclusive. In 25 control cycles where diagnosis of ovulation was possible by all 3 criteria, all were positive. Where at least 2 indices were available (in 37 of a total of 40 control cycles), likewise a 100 per cent incidence of ovulation was indicated. Thus, by applying either 2 or 3 criteria, 100 per cent of the premedication cycles were positive for ovulation. In contrast to these control data, in not a single one of the 71 cycles of medication with compound I were 2 available diagnostic criteria judged to be positive for ovulation. Likewise, in 29 cycles of medication with compound II, there was not even one instance in which a positive diagnosis could be made on the basis of all 3 criteria. When only 2 criteria were available for compound II (in 38 cycles), a positive diagnosis was recorded in 2 instances.



In both of these, however, the more direct test of ovulation, determination of pregnanediol excretion, showed a value of only 0.2 mg. per day, clearly a sub-normal amount.

2. *Morphologic evidence of ovulation (operative series):* In an attempt to obtain less questionable evidence of the effect of these synthetic steroids on ovulation, observations were made of the ovaries of 7 women (not in the series of 50) who had taken compound I for 1 to 3 months prior to required laparotomy. In 5 of these, the endometria were also examined.

Operation was performed on 2 patients because of tubal obstruction; on 4, because of long-standing infertility; and on one, because of endometriosis which did not interfere with ovarian function.

These patients, whose ages ranged between 28 and 32 years, had failed to conceive despite regular menses with 24 to 31 day cycles (mean,  $27.9 \pm 1.1$ ) and exposure of 2 to 10 years (mean,  $6.0 \pm 2.0$ ). Moreover, during the investigation of their infertility, before medication, temperature graphs had revealed regular biphasic curves, and endometrial biopsies obtained in the postovulatory phase were all of normal secretory type.

The time of operation, with reference to medication, is shown in Table II, as are the salient findings.

In 2 of these patients, the ovaries appeared small and sclerotic. In 3, gross follicles were found; none were observed in the remaining 4. No stigmas of recent corpora lutea were seen in any of the 7 operative cases. Three specimens showed evidence of late regressing corpora lutea characteristic of some preceding cycle.

Endometrial curettings were obtained from 5 of the 7 patients. Four disclosed the atypical changes described below in the nonoperative cases. The fifth specimen showed atypical secretory exhaustion in glands which, for the most part, were small and straight, but the stroma was well advanced toward decidua. Yet in this case, as in the others, no recent corpus luteum was seen grossly in either ovary. In the ovarian biopsy, however, one follicle was found by microscopic examination to have ragged granulosa and rather extraordinary enlargement and vacuolization of the theca interna. One may contemplate the possibility that progesterone or a precursor from the theca was supplemented by the administered steroid to evoke the strange progestational condition of the endometrium.

Whereas in 2 of 5 ovarian biopsies there seemed to be a normal number of primordial follicles, in 3 these appeared to be scant. In 2 of the latter cases, treatment had been given for one cycle, and in one case for 3 cycles. Could compound I, and so perhaps similar steroids, have a destructive effect, not only on mature, but also on primordial follicles?<sup>14</sup> None of these were seen in process of regression. Such problematical reduction of follicles was not immediately evidenced in the characteristics of menses following medication, nor in the subsequent fertility of 7 nonoperative patients similarly treated, as mentioned later.

*E. Details of Endometrial Response to Medication With Compounds I and II.*—In the immature, estrogen-primed rabbit, compounds I, II, and III all manifest progestational activity when administered orally.<sup>4, 5</sup> Likewise we have observed a similar progestational effect with the use of these steroids in estrogen-primed amenorrheic women (unpublished data). For these reasons the nature of the endometrial response in the patients of our series is worthy of comment. Never did we find a biopsy specimen which showed a *completely typical* secretory endometrium at a time in the treated cycle when it might be expected.

The more striking effects of compounds I and II on the endometrium, in contrast to those found at the comparable phases of the normal cycle,<sup>8, 10</sup> are illustrated by Figs. 3 to 6. The over-all picture, as depicted in endometrial

biopsies taken between cycle days 19 and 24 in 90 cycles, is of markedly increased progestational change in the stroma and a discernible increase in number and caliber of the venules. On the other hand, most glands are either hypoplastic or in a condition suggestive of mid-proliferation. In a very few biopsies there is isolated minimal or moderate evidence of secretory activity. Furthermore, there is in all instances strong implication, in the thinness of the tissues obtained for examination, that the normal growth stimulus from

Fig. 3.

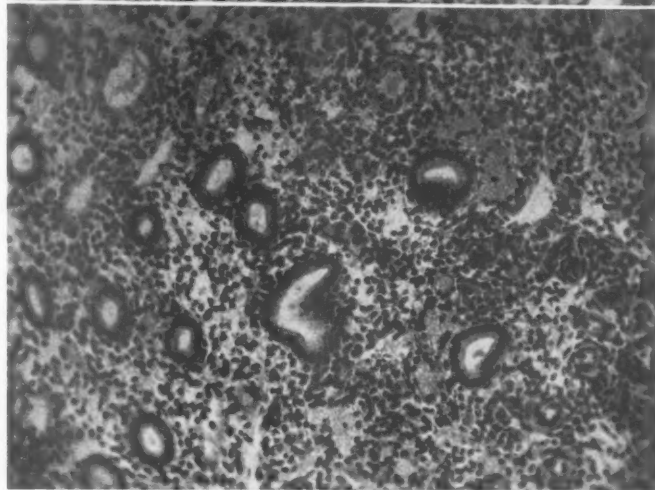
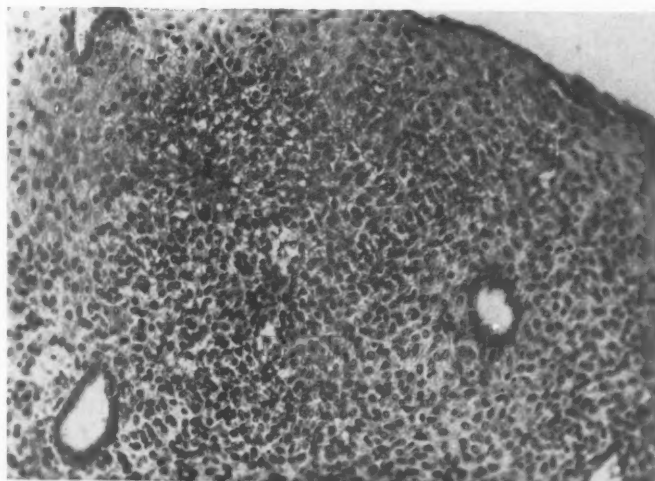


Fig. 4.

Fig. 3.—Case No. 55,350. Biopsy No. 56-795. Effect of compound I (5 mg. per day) on endometrial histology. Biopsy on sixteenth day of treatment (first treated cycle). Simple, early proliferative glands. Focal areas of highly developed predecidua. ( $\times 200$ ; reduced  $\frac{1}{4}$ .) (From Rock, García, and Pincus.<sup>3</sup>)

Fig. 4.—Case No. 55,350. Biopsy No. 56-2187. Effect of compound I (10 mg. per day) on endometrial histology. Biopsy on sixteenth day of treatment (third treated cycle). Simple, early proliferative glands; pseudocuboidal epithelium. Stroma cells, on the contrary, resemble those of mid-secretory phase with large, pale nuclei and moderate amount of cytoplasm. ( $\times 200$ ; reduced  $\frac{1}{4}$ .) (From Rock, García, and Pincus.<sup>3</sup>)

developing follicles is sharply curtailed or neutralized, or that such follicles are not present. At a dosage of 10 to 40 mg. per day of compound I, the signs suggestive of ovulation could be recognized in but 4 per cent of 50 biopsies taken in what might be considered the patient's habitual postovulatory phase. At

even 5 mg. per day of I, no positive indication was found in 9 cycles. With doses of 10 to 20 mg. per day of compound II, only 7 per cent of 28 biopsies were thought suggestive of ovulation. As by temperature graphs, and now by endometrial examination, we are led to suspect that ovulation was inhibited in at least a very high proportion of cases.

Fig. 5.

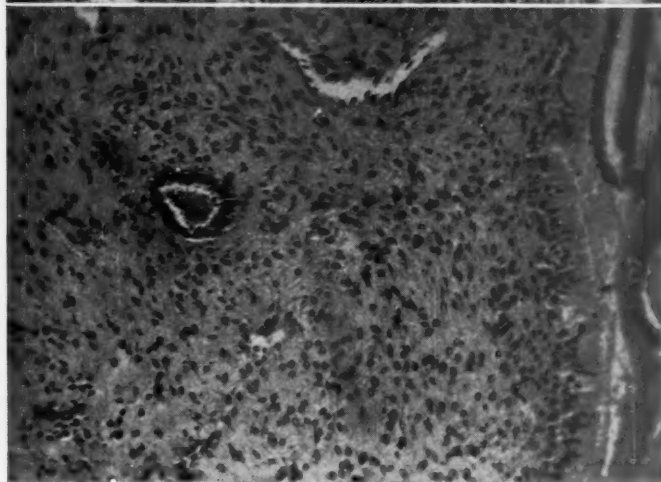
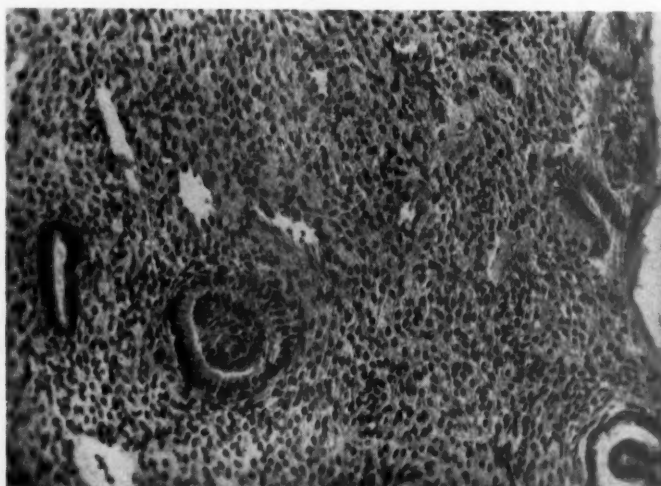


Fig. 6.

Fig. 5.—Case No. 53,404. Biopsy No. 56-2188. Effect of compound I (10 mg. per day) on endometrial histology. Biopsy on seventeenth day of treatment (third treated cycle). Simple glands with mid-proliferative epithelium. Venues increased in number and caliber. Stroma closely resembles that of late secretory phase. ( $\times 200$ ; reduced  $\frac{1}{4}$ .) (From Rock, Garcia, and Pincus.<sup>3</sup>)

Fig. 6.—Case No. 55,002. Biopsy No. 56-1787. Effect of compound II (10 mg. per day) on endometrial histology. Biopsy on fifteenth day of treatment (third treated cycle). Decidua-like stroma of cervix, probably of internal os. ( $\times 200$ ; reduced  $\frac{1}{4}$ .) (From Rock, Garcia, and Pincus.<sup>3</sup>)

### Compound III.—

The data on the 10 patients who received compound III have been grouped separately because the reactions to this steroid differed from those to compounds I and II. As with these latter, so with III, a significant decrease in the frequency values of positive ovulation indices and of pregnanediol output indicates inhibition of ovulation. There was no significant change in the mean length of the cycle, in 17-ketosteroid or in creatinine excretion.

Although the mean length of the cycle was essentially unchanged by the use of compound III, 8 of the 16 cycles were quite aberrant. One, on a 20 mg. per day dose, was 53 days in length with vaginal spotting from day 12 to day 28. Two cycles lasted for 11 and 13 days, respectively, with clear break-through bleeding. And, although the remaining 5 cycles were of normal length (mean, 27.6 days), 4 of these were characterized by vaginal spotting for 2 to 16 days, and one by slight staining throughout the cycle. Interval bleeding did not appear to be related strictly to dosage: the 2 frank break-throughs occurred on 20 and 30 mg. per day, respectively, and the others on daily doses of 10 to 40 mg., whereas those women who showed no interval bleeding had received 30 to 50 mg. per day.

On the basis of these data alone, we would conclude that compound III is an effective ovulation inhibitor, but that its ability to sustain endometrial tissue is limited. Endometrial biopsies after treatment with compound III disclosed hypoplasia, and in half the cycles there was break-through bleeding or spotting. All this suggests estrogen deprivation.

*Side Effects.—*

The number of patients who reported untoward symptoms is very small. When each type of side reaction is reviewed with respect to its incidence, the statistical significance becomes meaningless, if not deceptive. More accurate evaluation of these effects would require the use of placebos with "double blind" administration. The requirement that these also inhibit ovulation makes such a procedure impractical.

Trends in side effects of the 3 steroids may be summarized as follows: (a) a gain in weight associated with the use of all 3 compounds, particularly III; (b) mild breast symptoms, more with compound II; (c) fatigue, especially with compounds I and II; (d) neuromuscular effects with compound III; (e) nausea in a very few instances with compounds I and II; (f) a greater frequency of sex desire with compound II; a slight decrease with compounds I and III.

In order to avoid complicating the matter through subjective feelings of the patient, no attempt was made to question the individual during therapy. However, any spontaneous complaints tendered by the subjects were recorded. Furthermore, 2 to 3 months after cessation of medication, 38 of the women were questioned in detail with regard to pelvic, breast, metabolic, and other symptoms. Eleven\* patients on compound III were weighed at each visit to determine the effect on body weight of this steroid. Since, in most instances, no detailed record of weights was kept on patients taking I and II, impressions of weight change, as estimated by fit of clothing, rings, or shoes, often served to evaluate gain or loss.

*A. Weight Changes.*—Of the 11 women on compound III who were weighed routinely, 10 showed a definite weight gain, ranging from 3 to 13 pounds (mean, 6 pounds), after one to 3 cycles of therapy. In the single exceptional case, there was a loss of 8.5 pounds after 2 cycles of medication.

Follow-up questioning of the patients who had taken I and II likewise disclosed a gain in weight in some cases (4 out of 14 on I, and 4 out of 13 on II). Three patients on I, however, reported a loss in weight. It was characteristic of all 3 steroids that the patients who noted an increase in weight during medication lost most of this during the first few days of flow.

*B. Breast Symptoms.*—Breast symptoms, in the form of pain, engorgement, or tenderness, constituted another complaint, particularly within the group

\*In addition to the 10 women who comprised the compound III group, an eleventh patient, who had received III for only one cycle, was included in the study of side effects evoked by this steroid.



that had received compound II. Four out of 13 patients had this reaction, while only one patient in each of the other 2 medication groups suffered such discomfort.

*C. Fatigue.*—Fatigue was reported in 6 of 14 patients on compound I; 5 of 13 women on compound II; but in only 2 of 11 on compound III.

*D. Neuromuscular Effects.*—Depression, irritability, and nervousness, not unlike the symptoms associated with premenstrual tension, were mentioned by 5 of 11 who had taken compound III. Muscle spasm in the extremities, particularly upon sudden movements, was reported in 4 of 11 patients on compound III. None of these neuromuscular complaints were elicited from women on compounds I or II.

*E. Nausea.*—Nausea was previously reported by Greenblatt<sup>15</sup> in one of 16 women who received compound I. In the 50 patients of this study, only 2 of 29 on compound I, and one of 17 on compound II noted transient nausea.\* The latter complained of a "gagging" sensation during the first part of the second cycle of treatment. The transient nausea experienced by one of the women on compound I occurred during the first cycle, but not in subsequent ones, while the other patient had dizziness and nausea after breakfast during the first week of treatment in the second cycle. None of those taking compound III reported nausea.

*F. Effects on Libido.*—A diminution in libido was observed by more patients on compounds I and III than on compound II; indeed, with the latter steroid, there appeared to be a greater incidence of augmented sex desire. Four of 14 patients on compound I, 2 of 13 on compound II, and 5 of 11 on compound III reported loss of libido. Increase of libido, on the other hand, was not experienced by any of the 14 on compound I, whereas 4 of the 13 on compound II, and one of the 11 on compound III did note it.

TABLE III. EFFECT OF COMPOUNDS I AND II ON LENGTHS OF CYCLES AND ON OVULATION IN POSTTREATMENT CYCLES

CYCLE	NO. OF PATIENTS	MEAN CYCLE LENGTH (DAYS)	OVULATION BY BASAL TEMPERATURE			
			NO.	MEAN DAY	% ±	% -
Control premedication	40	27.2 ± 0.51	38	13.7 ± 0.31	6	6
First after medication with I	17	<u>32.4 ± 0.50*</u>	17	<u>17.2 ± 0.73</u>	11	6
Second after medication with I	11	<u>29.5 ± 0.79</u>	9	14.9 ± 1.11	20	0
Third after medication with I	7	30.0 ± 1.44	8	13.8 ± 0.95	0	0
First after medication with II	11	<u>35.2 ± 0.70</u>	10	<u>21.5 ± 1.46</u>	20	0
Second after medication with II	8	27.5 ± 1.58	8	12.5 ± 0.65	0	0
Third after medication with II	4	26.0 ± 1.58	4	14.5 ± 1.96	0	0

\*Underlined values differ significantly from the control.

### Follow-up Study

#### *Postmedication Effects on Menstruation and Ovulation.*—

*A. Length of Cycle, Time and Incidence of Ovulation.*—A limited follow-up study has been conducted with 28 patients who had received compound I or II, in most cases for 3 cycles. Lengths of cycles and basal body temperatures

\*The apparent discrepancy here, i.e., a total of 46 women who received I and II, is due to the fact that 4 of the 40 women of the I-II group (Table I) had both I and II, so they were counted here twice; also 2 others were included from the III group, who each had I for one cycle.



were recorded in one to 3 cycles following medication. In Table III are presented the data on lengths of cycles and time and incidence of ovulation as determined by basal body temperature graphs.

These data indicate that (1) there is a significant average increase in the length of the cycle immediately following medication with either compound, and that this increased cycle length prevails in the second cycle after medication with I; (2) a significant delay in ovulation time is observed in the first post-treatment cycle with each substance; and (3) there is some increase in the frequency of doubtful ( $\pm$ ) diagnoses of ovulation time in the first cycle after treatment with I and II, as well as in the second after I, but these increases are not statistically significant. If we group together the data on postmedication cycle lengths for I and II, the mean first, second, and third postmedication cycle lengths become  $33.5 \pm 0.49$ ,  $28.7 \pm 0.81$ , and  $28.6 \pm 1.22$  days, respectively. Statistically significant declines in the second and third cycles over the first occur on this basis, whereas the control cycle value differs significantly only from the first, not from the second and third posttreatment cycles.

*B. Duration of Flow and Latent Period to Flow.*—This observation of a significant effect on the length of the first postmedication cycle led us to examine our data on duration of flow in cycles before, during, and after medication with all 3 compounds, as well as the latent period from cessation of medication to the initiation of menstrual bleeding in the treatment cycles. As seen in Table IV, these data demonstrate a significant shortening of the period of flow during medication with I, but not with II or III. Following therapy with I, there was a return to the premedication duration. This effect of I is reflected in the values for the standard deviations which indicate also a significantly greater spread of flow deviations during medication; this returns to normal after treatment. It is notable, too, that the latent period to withdrawal bleeding is significantly longer in patients receiving I than in those taking II or III.

TABLE IV. EFFECT OF SYNTHETIC PROGESTINS ON DURATION OF MENSTRUAL FLOW AND LATENT PERIOD TO FLOW

CYCLES STUDIED	NO. OF CYCLES	MEAN DURATION OF FLOW (DAYS)	LATENT PERIOD TO FLOW (DAYS)	STANDARD DEVIATION
Pre-I	38	$4.39 \pm 0.185$	—	$0.994 \pm 0.133$
I	69	$3.62 \pm 0.169^*$	$2.51 \pm 0.167$	$1.405 \pm 0.118$
Post-I	39	$4.36 \pm 0.181^\dagger$	—	$1.064 \pm 0.121$
Pre-II	15	$4.07 \pm 0.267$	—	$1.033 \pm 0.189$
II	40	$4.28 \pm 0.178$	$1.79 \pm 0.188$	$1.123 \pm 0.126$
Post-II	16	$4.69 \pm 0.323$	—	$1.293 \pm 0.228$
Pre-III	11	$4.91 \pm 0.368$	—	$1.221 \pm 0.260$
III	13	$4.08 \pm 0.399$	$1.43 \pm 0.406$	$1.441 \pm 0.283$

\*Underlined values differ significantly from their premedication controls.

†Dashed values are significantly different from the medication values.

#### *Effects on Fertility.*—

We have been able to determine the incidence of pregnancy within 5 months following cessation of medication in the 38\* subjects of this study who received only I and/or II (Table V). In this group of 38, 7 pregnancies occurred. Six of these women had received medication for 3 cycles each; and one, for only one cycle. Three patients received only I, 2 received only II, and 2 others had taken II followed by I. Two conceived in the first postmedication cycle, 2 in the third, 2 in the fourth, and one in the fifth.

\*Two of the total 40 were omitted as they were treated with compound III also.

The quality of the infertility and the duration of exposure to conception in the total group of 50 women prior to therapy have already been discussed (Fig. 2). There was exposure in every treated cycle, yet no pregnancy occurred even though 4 habitual aborters were included. Conversely, 7 (18 per cent) of the 38 patients who had received I and/or II conceived within 5 months after treatment. Two of these, however, had been infertile for only 18 months of exposure before medication, so their conceptions are not of significance; if these 2 are omitted, the corrected percentage is 14 (5 pregnancies in 36 patients) within 4 months of cessation of medication. These 5 pregnancies are noteworthy, for they occurred in patients who had been infertile during exposure periods of, respectively, 3, 4½, 4½, 5, and 6 years.

TABLE V. PREGNANCIES FOLLOWING ORAL TREATMENT WITH COMPOUNDS I AND/OR II

PATIENT	AGE	TYPE OF INFERTILITY	EXPOSURE (YEARS)	COMPOUND	DOSAGE (MG./DAY)	NO. OF TREATED CYCLES	CYCLE DAYS OF MEDICATION	NO. OF CYCLES BETWEEN CESSATION OF THERAPY AND CONCEPTION
Al.	26	Secondary	1½	II	20	3	5-25 5-25 5-22	5
Pr.	32	Secondary	1½	II I	10 2.5*	2 1	5-25 6-24	3
Ga.	32	Primary	3	I I	5 10	1 2	5-25 5-25	1
Gr.	37	Primary	4½	I	5	3	5-25†	4
Ha.	29	Primary	4½	I I	20 10	1 2	10-30‡ 10-30	3
Ma.	29	Primary	5	II I	20 20	1 2	6-25 5-25	4
Pa.	30	Primary	6	II	20	1	5-25	1

\*Patient took low dosage by mistake. R was for 5 mg. per day.

†Omitted day 21 in second medication cycle.

‡Medication on days 10 through 30 due to patient's long cycles.

### Summary and Conclusions

In an effort to relieve inexplicable failure of reproduction in 50 women, one or another of 3 synthetic progesterone-like steroids was administered in dosages, ranging from 5 to 50 mg. per day, usually from the fifth through the twenty-fifth day of 3 menstrual cycles. These compounds, designated, for convenience, as I, II, and III, were, respectively, 17 $\alpha$ -ethinyl-19-nortestosterone, 17 $\alpha$ -ethinyl-5(10)-estraenolone, and 17 $\alpha$ -ethyl-19-nortestosterone. The effects of these 3 compounds on ovulation, menstruation, and fertility were evaluated.

1. When 2 indirect indices of ovulation were required, all 3 compounds gave evidence by temperature graphs and endometrial biopsies, or vaginal smears, of inhibition of corpus luteum development and, therefore, probably of ovulation during the cycles of treatment. That pregnanediol excretion was far below normal is strong confirmatory evidence of such inhibition.

Examination of the ovaries of 7 patients outside the regular series who had taken compound I failed to reveal any active corpora lutea, but raised a slight question of damage to primordial follicles. Although in the 50 patients not

operated upon this was not reflected in ovulation or menstruation in cycles immediately following treatment, yet the bare possibility of ovarian damage merits further study.

2. Neither during nor after therapy were there any troublesome effects on the incidence or duration of menstruation. Untoward symptoms of medication were relatively rare and mild.

3. Within 5 months following treatment of 38 patients with compound I and/or II, there occurred 7 conceptions, a relief rate of 18 per cent in this unpromising group. When this percentage is corrected by eliminating 2 pregnancies which followed exposure periods of only 18 months, the cure rate for the group of 36 patients is 14 per cent. This we think is more than can be attributed to chance when we consider the severity of the sterility and the short fixed period during which conception took place.

We are grateful to Dr. Luigi Mastroianni, Jr., and to Dr. John V. Kelly for their valuable clinical assistance.

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## PROGESTATIONAL AND ANDROGENIC SUBSTANCES TESTED ON THE HIGHLY PROLIFERATED VAGINAL EPITHELIUM OF SURGICAL CASTRATES

### I. Progestational Substances\*

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IN THE evaluation of endogenous hormonal conditions by cytological analysis, there are actually only two definitive diagnostic smear types: (1) those consisting of predominantly the superficial cornified cells, and (2) those consisting mainly of parabasal cells. The first cell type is diagnostic of marked estrogenic activity; the latter, of lack of estrogenic stimulation. All cells from the intermediate stages of proliferation may, however, be the result of various hormonal conditions which could include slight estrogenic activity, androgenic activity, or the activity of progestational agents. Therefore, the cytological interpretation of the intermediate states of proliferation is possible only if age, menstrual history, and data regarding the dosage and type of administered hormones are known to the interpreter of the cytological specimen.

During the normal menstrual cycle the greatest height of cellular proliferation is reached shortly before ovulation. At this time the smear will show an abundance of cornified superficial cells: most of these epithelial cells are flat and lie singly. Prior to ovulation, the first signs of regression of epithelial proliferation are observed<sup>1</sup>: the cells become less cornified and show more folding of the cytoplasm. As the luteal phase progresses, the cornified cells gradually disappear and the vaginal smear will contain primarily superficial noncornified or intermediate cells: most of these cells are folded and many are found in crowded clusters. By the premenstrual phase of the normal cycle, the vaginal smear will exhibit folded and crowded superficial noncornified or intermediate cells almost exclusively.

This regression of epithelial proliferation produced by the corpus luteum hormone has been classified in various degrees by Pundel.<sup>2</sup> Veziris and co-workers<sup>3</sup> studied cytologically the effects of administration of estrogens and progestational agents on the vaginal smears of postmenopausal women. Their results, although not uniform, do show that progestational therapy generally results in regression of epithelial proliferation.

\*This study was supported in part by the American Cancer Society, Institutional Grant, and by the Nathan Goldblatt Society Research Grant.



Analysis of vaginal smears has been used to determine the effects produced by various new substances with possible progestational activity.<sup>4-7</sup> This has been done by evaluating the degree of regressive epithelial changes observed after administration of test substances.

It was the purpose of the present study to test various progestational agents on the vaginal epithelium of 6 surgical castrates with the objective of determining the dosage of these substances necessary to induce luteal changes in the proliferated vaginal epithelium and endometrium of surgical castrates similar to or identical with those changes usually observed during the luteal phase of the normal menstrual cycle.

### Material and Method

This study was made on 6 patients aged 28 to 53, whose ovaries had been removed and whose intact uteri provided the material for histological examination. All patients had received permanent estrogen therapy or some type of cyclic hormone therapy since castration. Prior to this study, three artificial cycles were induced in all patients to ensure that secretory endometrial changes could be produced.

Originally the study was to have included 11 surgical castrates. Five were eliminated from the study because they did not cooperate or because of other factors, i.e., bacterial cytolysis, intercurrent infections, or irregular uterine bleeding, which would have precluded evaluation of therapy.

Throughout each 30 day test cycle, all patients received orally 1 mg. diethylstilbestrol daily to induce proliferative changes in the vaginal epithelium and endometrium. From the fourteenth day, various progestational substances were introduced. These were: (1) 17-alpha-hydroxyprogesterone caproate, administered by a single injection on the fourteenth day, (2) chemically pure progesterone, administered either by a single injection on the fourteenth day or by injection every other day from the fourteenth to the twenty-fourth day of the cycle, and (3) anhydroxyprogesterone administered orally from the fourteenth to the thirtieth day of cycle. The dosages, time intervals, and dates of administration for each patient are shown in Table I. "Day No. 1" of each test cycle in all cases was arbitrarily fixed as the first day following cessation of uterine bleeding. Vaginal smears were taken every third day of the cycle, fixed and stained by the method of Papanicolaou,<sup>8</sup> and cytologically evaluated. Endometrial biopsies were taken from each patient on the twenty-fourth to the twenty-ninth day of each test cycle. The effects of various dosages of 17-alpha-hydroxyprogesterone caproate, chemically pure progesterone, and anhydroxyprogesterone on the vaginal epithelium and the endometrium were studied and compared.

#### *Evaluation of the Vaginal Smear.—*

The cytological interpretation was made from a count of 300 cells from each vaginal smear. Fifty cells were counted from each of six random points in the smear. Only the areas where the cells were spread thinly on the slide were considered suitable for examination. The heavy clusters of cells resulting from a mechanical effect during preparation of the smears were omitted from this study.

The 300 cells counted from each smear were analyzed by use of three indices: (1) the karyopyknotic index, (2) the folded-cell index, and (3) the crowded-cell index. The acidophilic-cell index (percentage of acidophilic cells) sometimes used to evaluate estrogenic activity was omitted from this study because of the

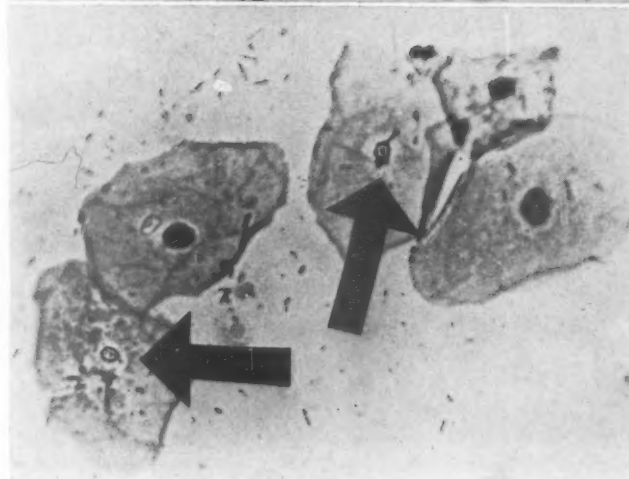
TABLE I. THE DOSAGES AND METHODS OF ADMINISTRATION OF THE THREE PROGESTATIONAL AGENTS USED IN THIS STUDY. ALL PATIENTS WERE RECEIVING IN ADDITION 1 MG. DIETHYLSTILBESTROL DAILY (ORALLY) DURING THE 30 DAYS OF EACH TEST CYCLE.

NO. OF PATIENT	AGE	YEARS POST CASTRATION	DOSAGES OF 17-ALPHA- HYDROXYPROGESTERONE ONE CAPROATE PARENTERALLY ADMINISTERED ON 14TH DAY OF CYCLE (MG.)	DOSAGES OF PROGESTERONE ONE PARENTERALLY ADMINISTERED EVERY OTHER DAY FROM 14TH TO 24TH DAY INCLUSIVE. (TOTAL DOSAGE IN PARENTERAL DOSES) (MG.)	DOSAGES OF PROGESTERONE GESTERONE PARENTERALLY ADMINISTERED ON 14TH DAY OF CYCLE (MG.)	DOSAGES OF ANHYDRO- HYDROXYPROGESTERONE ONE ORALLY ADMINISTERED DAILY DURING SECOND HALF OF CYCLE. (TOTAL DOSAGE IN PARENTERAL DOSES) (MG.)	DAY OF ENDOMETRIAL BIOPSY	DAYS OF UTERINE BLEEDING
1	28	2	62.5 125 250				26	32-38 32-36 32-35
2	42	12	62.5 125 250 375				27 24 27	32-36 33-38 31-36 31-35
3	48	16	125 250 500				27	33-38 32-37 31-36 32-37
4	53	13	250 375 500		500		26 26 26 26	32-36 32-37 31-38 32-38
5	37	6	500	100 (600) 50 (300) 25 (150) 100 (600)			26 26 26 26	32-37 33-37 32-36 32-37
6	36	10	125 250 500			50 (800) 100 (1,600) 200 (3,200) 300 (4,800)	27 27 27 29 29 29	32-37 32-36 32-36 33-38 33-39 32-37 32-36

variability of staining reaction due to external factors. Another commonly used index, the superficial-cell index, was not included in this assessment since the occurrence of deep cells was not expected.

1. The *karyopyknotic index* gives the ratio of squamous cells with pyknotic nuclei to those with vesicular nuclei. Theoretically, then, a karyopyknotic index of 100 per cent would mean that all exfoliated squamous cells contained pyknotic nuclei (maximal estrogenic effect). Phase microscopy is more reliable than the subjective method of selecting pyknotic nuclei with the bright-field microscope.<sup>8</sup>

A.



B.

Fig. 1.—A, Photomicrograph of 5 squamous epithelial cells in a vaginal smear. The smear is stained by the Papanicolaou procedure.

B, Photomicrograph of the same cells as shown in A, with microscope with phase contrast. Two of the 5 nuclei are truly pyknotic. The pyknotic nuclei shone a bright red due to a specific phaseoptical deviation of the light over dense corpora. (Zeiss Phasemicroscope;  $\times 40$ ; reduced  $\frac{1}{6}$ .)

The karyopyknosis of the cells was objectively standardized by use of a phase microscope (Zeiss Winkel,  $40\times$  magnification) on specimens fixed and stained after the method of Papanicolaou<sup>9</sup> (Fig. 1). The karyopyknotic index is considered the most reliable cellular index for the determination of estrogenic activity.<sup>11</sup>

2. The *folded-cell index* is the ratio of folded cells from the superficial and intermediate layers to the flat cells from the same layers (Fig. 2).

3. The *crowded-cell index* is the ratio of crowded cells from the superficial and intermediate layers to single-lying squamous cells from the same layers. When more than 3 cells overlapped in a cluster they were considered to be crowded (Fig. 3).

Fig. 2.

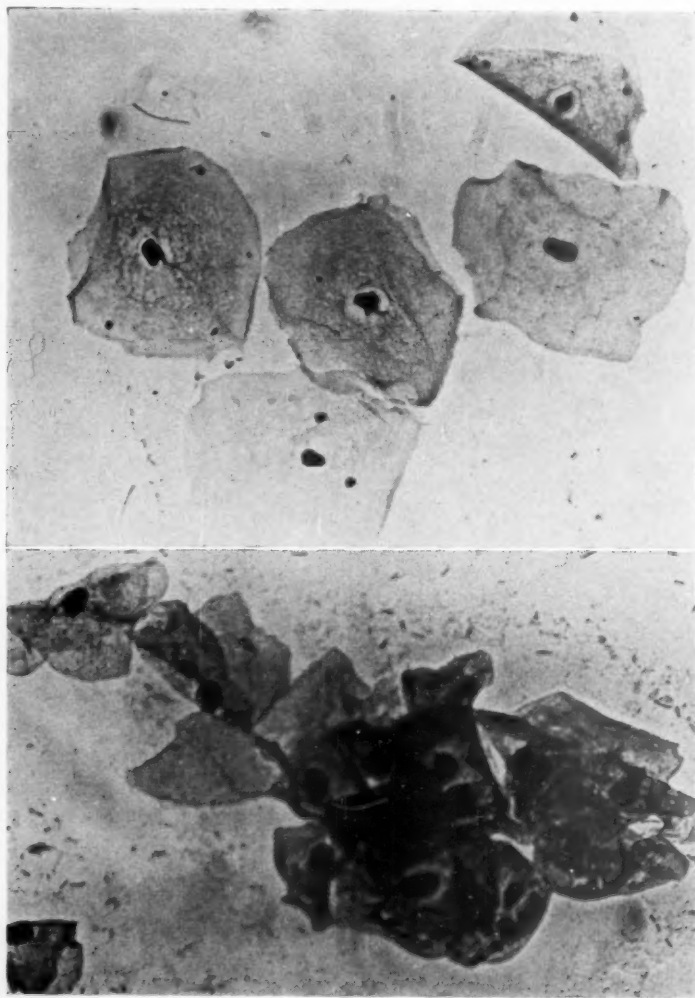


Fig. 3.

Fig. 2.—Four flat superficial squamous epithelial cells and one folded superficial cell. The photomicrograph was prepared from a vaginal smear of a surgical castrate who was treated with 1 mg. diethylstilbestrol daily (orally) during the last 14 days.

Fig. 3.—Folded and crowded squamous epithelial cells. The photomicrograph was prepared from a vaginal smear of the same surgical castrate as shown in Fig. 2, 12 days after intramuscular injection of 375 mg. 17-alpha-OH-progesterone caproate. The administration of estrogen, 1 mg. diethylstilbestrol daily, was continued simultaneously.

The degree of epithelial regression from the fully proliferated state has been arbitrarily classified below to facilitate interpretation (Fig. 4). These groups are:

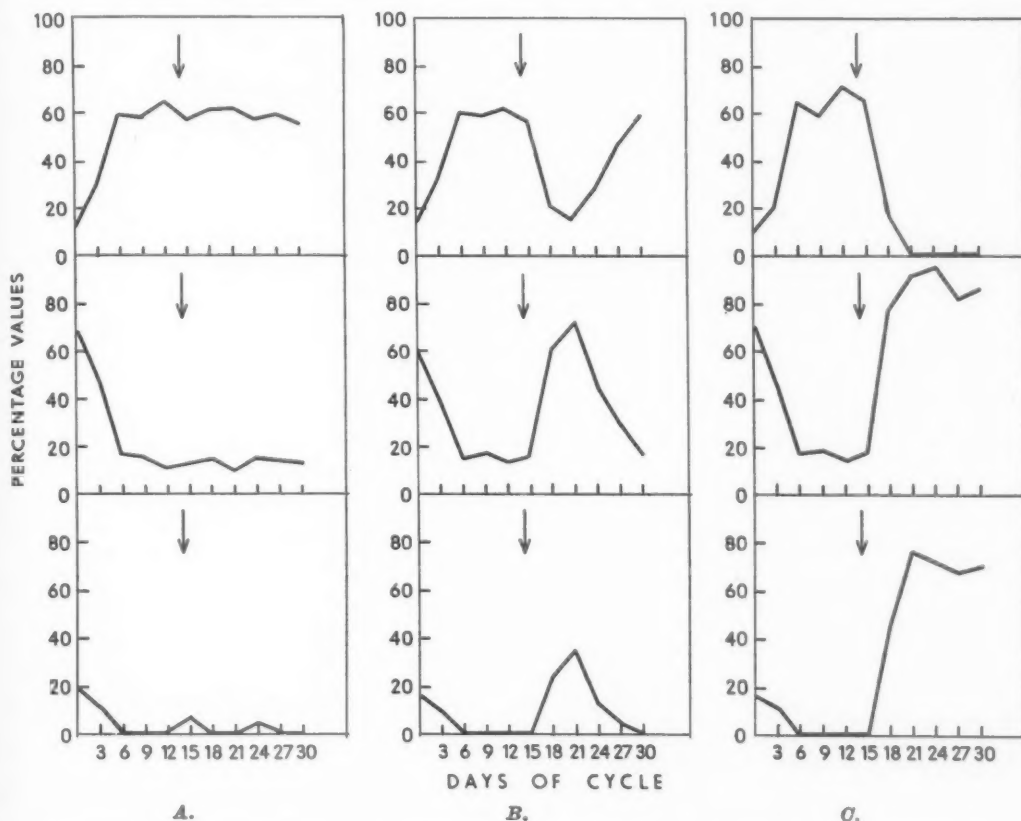
- (1) —, no regression.



(2) +, moderate regression: to noncornified superficial cell layers with a few cells of the intermediate cell layers in evidence. Most of the cells show folding, but not all cells appear in crowded clusters.

(3) ++, marked regression to the cell type usually observed during the middle or late luteal phase of the normal menstrual cycle, i.e., crowded and folded noncornified superficial and intermediate squamous cells.

The duration of cytological regression is considered as the period of time during which the progestational substance produces an active regressive effect upon the vaginal epithelium. It is reckoned from the day when this epithelial change is first detected to the day when the cellular pattern begins its recovery to the initial state of proliferation.



A single intramuscular injection of 62.5 mg. 17-alpha - hydroxyprogesterone caproate on the fourteenth day of the test cycle.

A single intramuscular injection of 125 mg. 17-alpha - hydroxyprogesterone caproate on the fourteenth day of the test cycle.

A single intramuscular injection of 375 mg. 17-alpha - hydroxyprogesterone caproate on the fourteenth day of the test cycle.

Fig. 4.—Graphs showing the degrees of cytological regression.

Representative karyopyknotic, folded-cell, and crowded-cell indices showing the degrees of response of the vaginal epithelium of surgical castrates, using various dosages of 17-alpha-hydroxyprogesterone caproate. (Each patient also received 1 mg. diethylstilbestrol daily throughout the test cycle.)

- (A) Response (-).
- (B) Response (+).
- (C) Response (++)

To facilitate evaluation and comparison of the degree and duration of cytological regression produced by the dosages of the three progestational agents, curves for karyopyknotic, folded-, and crowded-cell indices were plotted for every test cycle.

All the curves were plotted from the average results in the test cycles (Figs. 5, 6, 7). These average curves show no significant deviation from the curves obtained in the individual test cycles (Fig. 8).

The karyopyknotic index, folded-cell index, and crowded-cell index of normally menstruating women were plotted with the same technique. These are the standard curves with which all results are compared (Fig. 9).

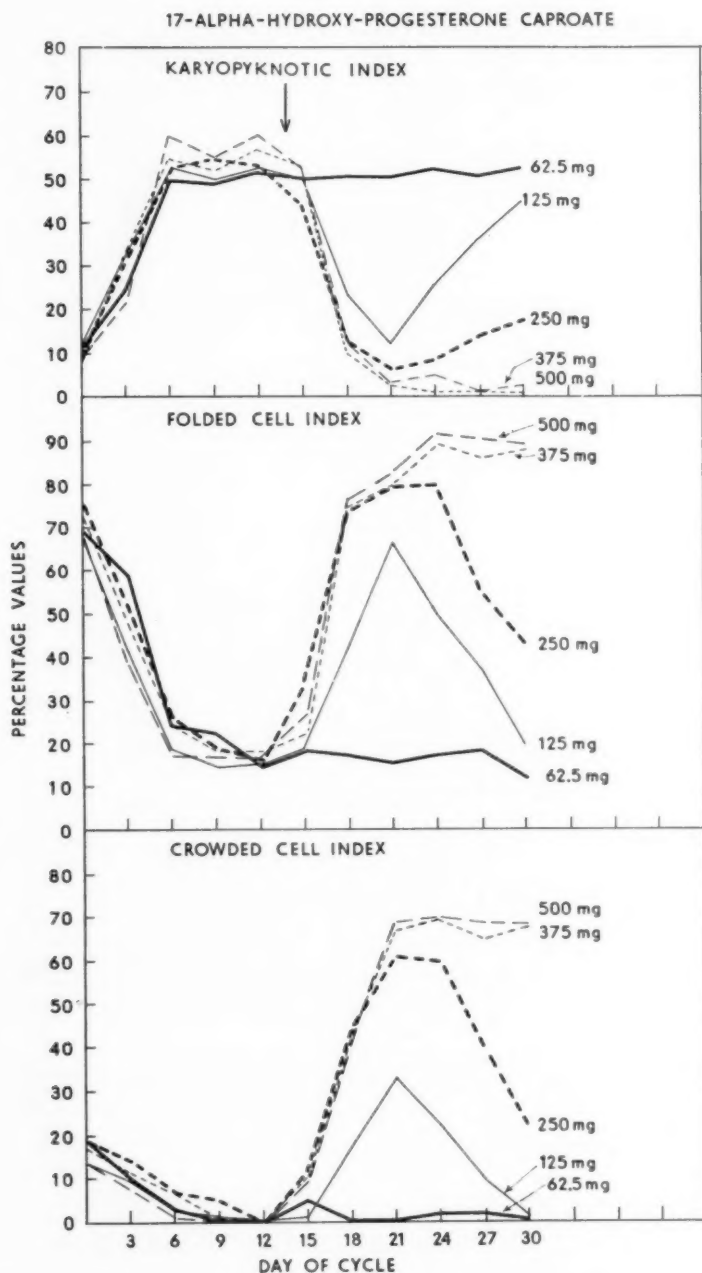


Fig. 5.—Average curves of the 3 cellular indices showing response of the vaginal epithelium of surgical castrates to various dosages of 17-alpha-hydroxyprogesterone caproate administered by a single injection on the fourteenth day of the artificial cycle. Each patient received daily 1 mg. diethylstilbestrol (orally) throughout the entire test cycle.

With reference to the presence or absence of secretory changes, four histological grades based on glandular structure are proposed:

(1) *Proliferative Phase, No Secretory Change*: All glands are in the proliferative phase; some may show evidence of prolonged estrogen stimulation.

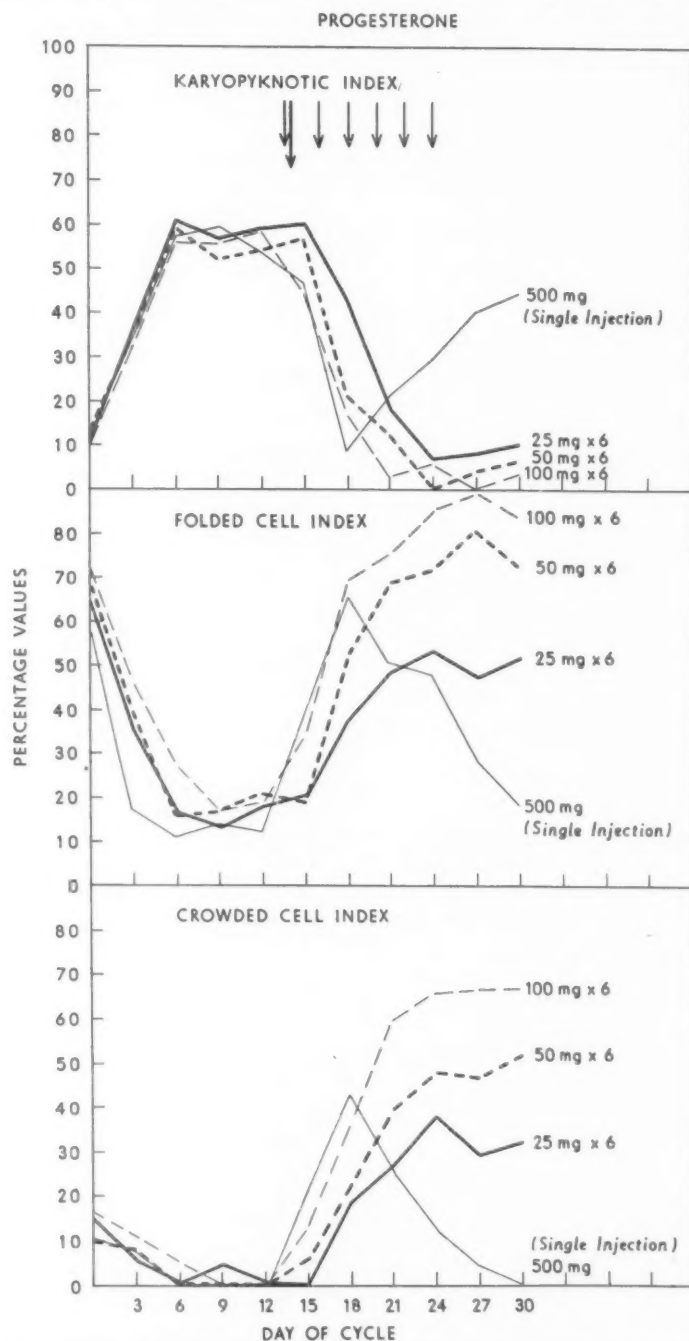


Fig. 6.—Curves of the 3 cellular indices showing the response of the vaginal epithelium of surgical castrates to various dosages of chemically pure progesterone, administered by six intramuscular injections on alternate days during the latter half of the test cycle (small arrows), or as a single intramuscular injection on the fourteenth day of the test cycle (large arrow). Each patient also received daily 1 mg. diethylstilbestrol (orally) throughout the entire test cycle.

(2) +, *Minimal Evidence of Secretory Change*: The minority of the glands examined show the presence of subnuclear vacuolation with central positioning of cell nuclei.

(3) ++, *Early (Delayed) Secretory Change*: There is definite evidence of a secretory change but not so far advanced as would be expected in a normal

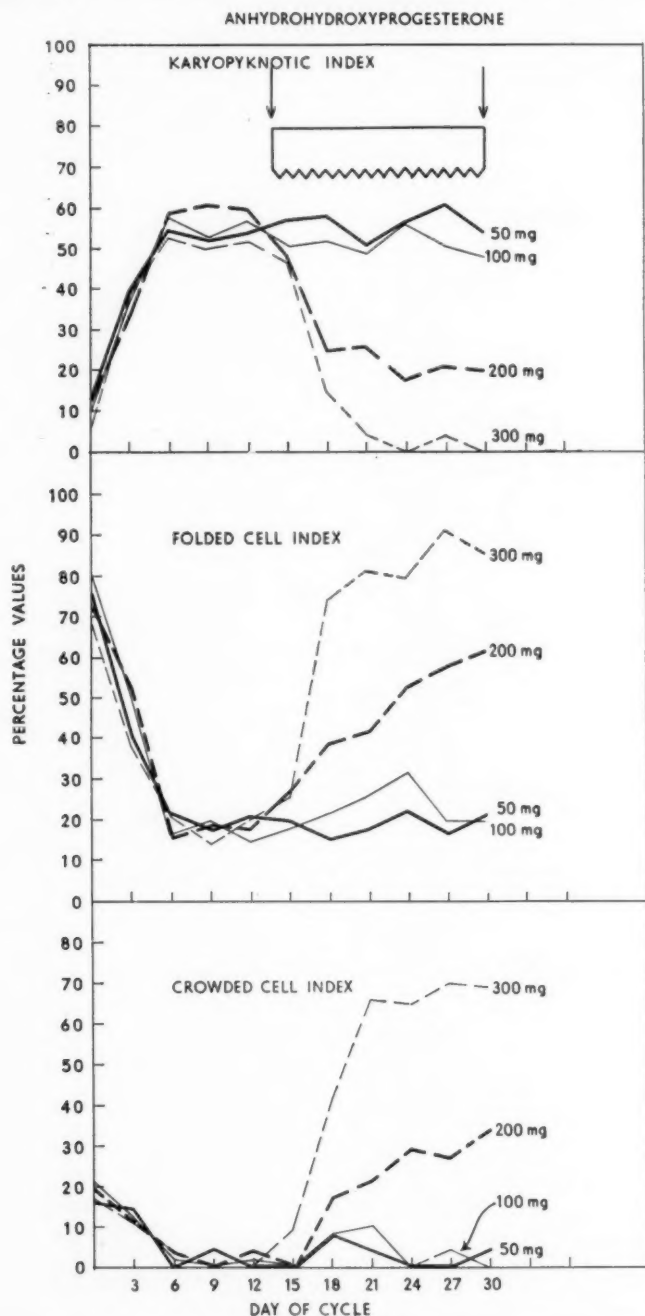


Fig. 7.—Curves of the 3 cellular indices showing the response of the vaginal epithelium of surgical castrates to various dosages of anhydrohydroxyprogesterone (oral). The period between the arrows indicates the duration of the daily progestational therapy. Each patient, in addition, received orally 1 mg. diethylstilbestrol daily throughout the 30 day test cycle.

menstrual cycle 14 days after ovulation. Subnuclear vacuolization is marked, some of the nuclei have moved to the bases of the cells, and there is minimal evidence of supranuclear vacuolization; accumulation of glandular secretion and partial loss of cellular edges may be in evidence.

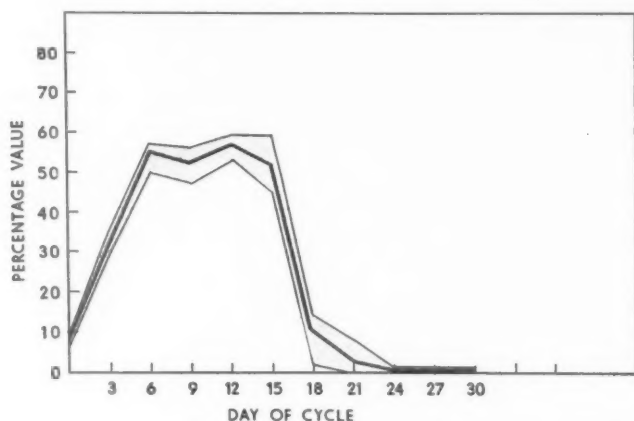


Fig. 8.—The heavy line represents the average value of the karyopyknotic index for 4 patients who received the same dosage (500 mg.) of 17-alpha-hydroxyprogesterone caproate. Maximal and minimal variations from the average are indicated by the shaded area.

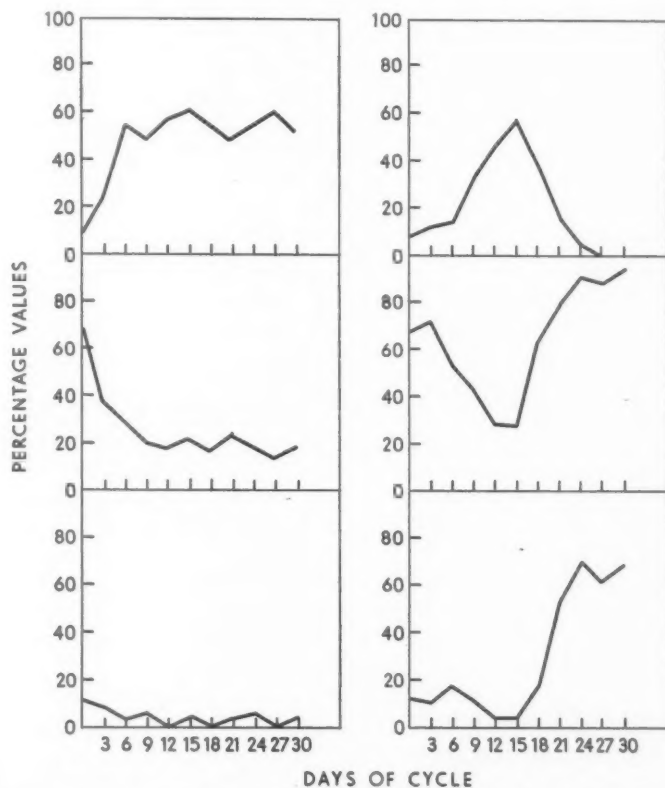


Fig. 9.—The 3 indices on the left show the cellular patterns of a 30 day test cycle of a surgical castrate receiving daily by oral administration 1 mg. diethylstilbestrol without progestational therapy. On the right, the 3 indices show the cellular patterns of a normal menstrual cycle.



(4) +++, *Marked Secretory Change*: There is marked tortuosity of glands, basal position of cellular nuclei, supranuclear vacuolization, loss of cellular borders, and accumulated secretion within the lumen of the gland.

The difficulty of evaluating small endometrial biopsies in this way is fully recognized. This arbitrary classification is an attempt roughly to standardize endometrial reports for easier reference (Table II).

TABLE II. THE CYTOLOGICAL AND HISTOLOGICAL EFFECTS RESULTING FROM ADMINISTRATION OF VARIOUS DOSAGES OF THREE PROGESTATIONAL AGENTS ON THE HIGHLY PROLIFERATED VAGINAL AND ENDOMETRIAL EPITHELIUM OF SURGICAL CASTRATES

TEST CYCLE	YEARS POST CASTRATION	DOSE (MG.)	CYTOLOGICAL RESPONSE	DURATION OF RESPONSE	DAY BIOPSY TAKEN	ENDO-METRIAL SECRETORY CHANGE
<i>17-Alpha-Hydroxyprogesterone Caproate.*—</i>						
6	2	62.5	—		26th	—
12	12	62.5	—		None	
19	16	125	+	6 days	None	
7	2	125	+	6 days	26th	+
13	12	125	+	6 days	27th	+
36	10	125	+	6 days	27th	+
26	13	250	++	6 days	26th	+
20	16	250	++	9 days	27th	+
8	2	250	++	9 days	26th	++
14	12	250	++	9 days	24th	++
37	10	250	++	9 days	27th	++
15	12	375	++	15 days	27th	+++
27	13	375	++	15 days	26th	++
21	16	500	++	15 days	27th	+++
35	6	500	++	15 days	26th	+++
38	10	500	++	15 days	27th	+++
28	13	500	++	15 days	26th	+++
<i>Anhydrohydroxyprogesterone.†—</i>						
39	10	50 × 16	—		29th	—
40	10	100 × 16	—		29th	—
41	10	200 × 16	+	15 days	29th	+
42	10	300 × 16	++	15 days	29th	+++
<i>Progesterone.‡—</i>						
22	16	500	++	3 days	27th	+
33	6	25 × 6	+	9 days	26th	++
32	6	50 × 6	++	9 days	26th	++
29	13	100 × 6	++	12 days	26th	+++
34	6	100 × 6	++	12-15 days	26th	+++

\*In all cases, the dosage was given as a single intramuscular injection on the fourteenth day. There is a fairly uniform response to a specific dose of 17-alpha-hydroxyprogesterone caproate, regardless of the age of the patient and the period of time since castration. Each patient was receiving in addition orally 1 mg. diethylstilbestrol daily throughout each 30 day test cycle.

†Daily dosages of anhydrohydroxyprogesterone were given orally from the fourteenth to the twenty-ninth day of each test cycle. In addition, the patient was receiving orally 1 mg. diethylstilbestrol daily throughout the 30 day test cycle. The same patient was used for all tests.

‡In test cycle No. 22, the patient received 500 mg. progesterone by a single intramuscular injection on the fourteenth day of the cycle. In all other cycles, the dosage was administered parenterally every other day starting at the fourteenth day for a 12 day period. In addition, each patient received orally 1 mg. diethylstilbestrol daily throughout the 30 day test cycle.

### Results (Table II)

A. *Vaginal Epithelium*.—Marked cytological regressive changes (++) identical in quality and duration with those seen in a luteal phase of a normal menstrual cycle are induced with a single intramuscular administration of 375 mg. 17-alpha-hydroxyprogesterone caproate on the fourteenth day. These regressive changes (folding and crowding of noncornified cells) persist for the entire second half of the test cycle. Treatment with 500 mg. 17-alpha-hydroxyprogesterone caproate by single intramuscular injection on the fourteenth day shows

little by way of significant change over the dosage of 375 mg. 17-alpha-hydroxyprogesterone caproate. Marked cytological changes are also induced for 15 days with oral administration of 300 mg. anhydrohydroxyprogesterone daily from the fourteenth to the thirtieth day of the artificial cycle (total dosage 4.8 Gm.). Marked cytological regression for 12 to 15 days' duration is induced in one out of 2 cases by 100 mg. chemically pure progesterone administered on alternate days during the second half of the test cycle (total dosage 600 mg.). In the other cases where 100 mg. progesterone was given on alternate days, marked cytological regression persisted for 12 days only.

Marked cytological regressive changes identical in quality but not in duration with those observed during a luteal phase of a normal menstrual cycle are induced for a period of 9 days in 4 out of 5 cases where 250 mg. 17-alpha-hydroxyprogesterone caproate is administered. In the remaining case, 250 mg. 17-alpha-hydroxyprogesterone caproate causes regression of epithelial proliferation for only 6 days. Six injections of 50 mg. chemically pure progesterone during the latter half of the test cycle induce marked cytological regressive changes for a period of 9 days. However, a single injection of 500 mg. chemically pure progesterone on the fourteenth day induces marked cytological regressive changes for a period of only 3 days.

Moderate cytological regressive changes (+) are present for approximately 6 days when 125 mg. 17-alpha-hydroxyprogesterone caproate is injected on the fourteenth day. When 200 mg. anhydrohydroxyprogesterone is taken orally each day of the latter half of the cycle (total dosage 3.2 Gm.) moderate regressive changes result. When 25 mg. progesterone is injected every other day beginning on the fourteenth day of the cycle (total dosage 150 mg.) moderate regressive changes occur over a period of 9 days.

No cytological regression is induced as a result of a single injection of 62.5 mg. 17-alpha-hydroxyprogesterone caproate on the fourteenth day, or after daily oral administration of 50 or 100 mg. anhydrohydroxyprogesterone during the latter half of the test cycle (total dosages 800 mg. and 1.6 Gm.).

**B. Endometrium.**—Endometrial secretory changes indistinguishable from those of a normal luteal phase (+++) are observed in all cases when 500 mg. 17-alpha-hydroxyprogesterone caproate is administered parenterally on the fourteenth day of the artificial cycle. The same results (+++) are obtained with 6 injections of 100 mg. chemically pure progesterone each on alternate days in the latter half of the test cycle (total dosage 600 mg.), and with oral administration of 300 mg. daily of anhydrohydroxyprogesterone (total dosage 4.5 Gm.) from the fourteenth day of the cycle. In one out of 2 cases where 375 mg. 17-alpha-hydroxyprogesterone caproate was administered on the fourteenth day, the same complete secretory changes are induced.

Early (delayed) secretory changes (++) are found in the other case following a single injection on the fourteenth day of 375 mg. 17-alpha-hydroxyprogesterone caproate. Three out of 5 cases respond with early (delayed) secretory changes when 250 mg. 17-alpha-hydroxyprogesterone caproate is injected on the fourteenth day. Six injections of both 50 and 25 mg. chemically pure progesterone during the latter half of the test cycle (total dosage 300 mg. and 150 mg.) produce early (delayed) secretory changes in the endometrium.

Minimal evidence of secretory change (+) in some glands and proliferation in the major portion of the endometrium are observed following a single intramuscular injection on the fourteenth day of 125 mg. 17-alpha-hydroxyprogesterone caproate, and in 2 out of 5 cases where 250 mg. 17-alpha-hydroxyprogesterone caproate is administered on the fourteenth day. Oral administration of 200 mg. anhydrohydroxyprogesterone daily from the fourteenth to the thirtieth day of the artificial cycle (total dosage 3.2 Gm.) also induced minimal secretory changes (+). The single injection of 500 mg. chemically pure progesterone on the fourteenth day caused these same secretory changes.

No secretory changes (-), but merely proliferation, are observed after the single injection on the fourteenth day of 62.5 mg. 17-alpha-hydroxyprogesterone caproate. Neither 50 nor 100 mg. anhydrohydroxyprogesterone taken daily (orally) throughout the second half of the artificial cycle induce any secretory changes in the endometrium (total dosage 800 mg. and 1.6 Gm.).

### Comment

The graphic results of this cytological assessment show that there is little or no significant individual variation in the response of all 6 surgical castrates to a particular dosage of a progestational substance. These findings are at variance with the results of Veziris and co-workers<sup>3</sup> who have shown that menopausal women do not react uniformly to artificial hormone stimulation. The same dosages of a drug induce almost identical results irrespective of the age of the individual and of the interval of time which has elapsed since castration. The changes induced in the vaginal epithelium of any one castrate reflect rather accurately the cytological changes which generally occur as the result of hormone therapy. It must be emphasized here, however, that this paper reports the observations made on 6 castrates from a total of 11 with whom the study was actually started. In 5 patients, the study was discontinued for the reasons stated previously.

The karyopyknotic index is the most reliable of the three indices for quantitative assessment of epithelial response to hormone stimulation. For practical purposes, however, the folded-cell index may be useful. Although not all cells with karyopyknotic nuclei are flat and not all folded cells will contain vesicular nuclei, the two indices may be considered relatively similar.

Karyopyknosis is not easily standardized with the bright-field microscope and individual examiners will have individual opinions as to what is a pyknotic and what is still a vesicular nucleus. For these reasons the use of phase microscopy<sup>8</sup> may eliminate subjective variation in the determination of karyopyknosis. By using the folded-cell index as an additional diagnostic check, it is possible to eliminate the individual variations of opinion which arise when the karyopyknotic index alone is used.

Of the three indices used, the crowded-cell index is the least accurate because (a) artificial crowding of cells prohibits accurate evaluation, and (b) an artificial line has to be drawn between crowded and single-lying cells, e.g., 3 cells lying over each other are classified arbitrarily as not crowded, whereas 4 cells lying over each other are classified as crowded.

The comparative analysis of smears and endometrial biopsies reveals a close parallelism between the induction of secretory changes in the endometrium and luteal changes in the exfoliated vaginal epithelial cells. It can be assumed, then, that marked luteal changes in the vaginal epithelial cells will occur if the dosage of the progestational agent is sufficient to induce complete secretory changes in the endometrium.

### Conclusions

1. Cytological changes characteristic of the luteal phase of the normal menstrual cycle can be induced by combined estrogen and progestational therapy.
2. Luteal changes in the vaginal epithelial cells identical in quality and duration with those observed in the latter half of the normal menstrual cycle can be induced in the highly proliferated vaginal epithelium (1 mg. diethylstilbestrol daily per os) of surgical castrates following a single injection of 375 to 500 mg. 17-alpha-hydroxyprogesterone caproate on the fourteenth day, or

after 6 consecutive injections of 100 mg. of progesterone (on alternate days during the second half of the cycle, total dosage 600 mg.), or after oral administration of 300 mg. of anhydrohydroxyprogesterone daily through the last 16 days of the cycle (total dosage 4.8 Gm.).

3. The above dosages of these progestational agents will also induce complete secretory changes in the endometrium which seem to occur simultaneously with characteristic luteal changes in the exfoliated vaginal cells.

4. The progestational dosages arrived at in this study are not intended as quantities for hormone therapy. They indicate only the relative amounts of the progestational agents necessary to suppress the given estrogen stimulation of 1 mg. diethylstilbestrol (per os) daily.

5. In surgical castrates, regardless of age, there seems to be a relatively uniform cytological response to progestational and estrogenic test therapy. The study is mainly significant, however, for its determination of the relative activity of various substances on the same test patients rather than for its determination of absolute replacement dosages.

### Summary

The effects of 17-alpha-hydroxyprogesterone caproate, chemically pure progesterone, and anhydrohydroxyprogesterone on the highly proliferated vaginal epithelium and endometrium of 6 surgical castrates were evaluated and compared.

It has been found that dosages of progestational agents sufficient to induce complete secretory changes in the endometrium indistinguishable from those in the secretory phase of a normal menstrual cycle also induce so-called luteal changes in the vaginal epithelium.

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## SENSITIVITY TO UNCONJUGATED PREGNANDIOL

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IN MAN, pregnandiol, the metabolic product of progesterone, is excreted in the urine in chemical combination with glucuronic acid. The pregnant rabbit also excretes pregnandiol glucuronide.<sup>1, 2</sup> Pregnanndiol has been extracted from the urine of many other species but whether or not it is excreted in conjugated form is not known.

In earlier work<sup>3, 4</sup> it has been shown that women may become allergic to pregnandiol and that the common clinical manifestations of the allergy are numerous disorders related to the menstrual cycle, pelvic (ovarian) pain, painful breasts, premenstrual tension, dermatoses, etc. The sensitivity is demonstrated by the occurrence of skin reactions and by the aggravation and production of the symptoms by the steroid. It has further been shown that rabbits and guinea pigs can be sensitized to pregnandiol; allergic skin reactions are observed in a high percentage of animals after preliminary sensitization with the steroid mixed with a suitable adjuvant.<sup>5</sup>

A reasonable hypothesis to explain the occurrence of allergy to this endogenous substance is that the conjugation of pregnandiol with glucuronic acid is a protective mechanism, and that failure of conjugation in susceptible individuals may result in the development of allergic reactions.

Allergy to pregnandiol is objectively demonstrated by skin test. In the majority of sensitive patients the reaction is delayed, reaching a maximum in about 24 hours. There are patients, however, whose sensitivity is so great that classical intracutaneous reactions to minute quantities of pregnandiol occur immediately. The seven-year history of such a patient is reported. Repeated local and systemic reactions to the intracutaneous injection of pregnandiol were observed. The excretion in the urine of both conjugated and unconjugated pregnandiol was determined during a pregnancy, when a remarkable correlation between the spontaneous occurrence of severe symptoms and the amount of free pregnandiol excreted in the urine was found.

Just as a case of extreme sensitivity to any common allergen such as house dust or coconut throws light on the common problem of allergy to these substances, so this case helps to elucidate the common gynecological disorders related to the menstrual cycle, pelvic pain, premenstrual tension, etc. Sensitivity to pregnandiol is as prevalent as hay fever but it is difficult to demonstrate convincingly because the offending substance is endogenous.

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B. E. C. (No. 1811) is a 30-year-old graduate nurse. Since the fall of 1949, incident to some months' residence on the west coast of the United States, she had infrequent menstruation and episodes of pain in the right lower quadrant, nausea and vomiting and, in severe attacks, inability to empty the bladder. She had begun to menstruate at 14 and, until the irregularity began, had a 30 day cycle with a flow of 4 days. There had been occasional Mittelschmerz, right lower quadrant pain of short duration in midcycle, previous to the oligomenorrhea. Her appendix had been removed at the age of 20 because of right lower quadrant pain, nausea and vomiting. The pathological diagnosis was "recurrent appendicitis."

Menstruation occurred in October, 1950, and was preceded for 2 or 3 days by crampy pain in the right lower quadrant, nausea and vomiting, which continued through the first 2 days of the flow. Thereafter, episodes of pain accompanied by nausea and vomiting and, when persistent, by retention of urine, occurred irregularly. They were at times followed by menstruation. The patient was hospitalized during some of the more prolonged episodes when a retention catheter was necessary. Except for the finding of a hypotonic bladder, results of physical and neurological examinations were within normal range. Various tests and assays of blood and spinal fluid resulted in no diagnostic findings. Skin tests with common allergens were all negative. Phenolsulfonphthalein excretion was 87 per cent in 2 hours. Urinary infection was present at times but pyelograms remained normal and the infection cleared promptly when the urinary retention abated.

An endometrial biopsy taken on the first day of one of the infrequent menstruations following a 2 week episode of acute symptoms showed progesteronally proliferated endometrium indicating that progesterone and, therefore, pregnandiol had been present during the time she was having symptoms. Two biopsies taken when there was the unusual occurrence of prolonged bleeding in addition to the pain and other symptoms showed incompletely developed progesterational endometrium, again indicating that progesterone was present, some of which was being metabolized to pregnandiol.

During an episode of pain, nausea, vomiting, and retention of urine in 1952, skin tests were done with steroid hormones and their metabolites. Aqueous suspensions of cortisone, estradiol, estriol, estrone, pregnandiol, pregnenolone, progesterone, and testosterone, 0.1 mg. in 0.1 ml., were given subcutaneously. In 24 hours, there was a marked reaction to pregnandiol and slight reactions to estrone, progesterone, and pregnenolone. The reaction to pregnandiol reached a maximum in 48 hours. There was an area approximately 10 by 7 cm. of extreme tenderness, swelling, erythema, and heat.\* It was accompanied by aggravation of the symptoms. Later, a test with pregnandiol, 0.000001 mg. in aqueous suspension, elicited a reaction. Attempts at hyposensitization with pregnandiol were without effect. Nothing was achieved but aggravation of the patient's symptoms. Intracutaneous tests were not attempted at this time.

On Nov. 16, 1955, she was seen for the first time in 21 months during which time she had been living elsewhere. The pattern of oligomenorrhea with irregular episodes of pain and other symptoms had continued. During one of the episodes of pain, a laparotomy had been done. The pelvic organs were found to be normal. During much of the previous year, menstruation had been at intervals of approximately three months and symptoms were limited to right lower quadrant crampy pain and nausea beginning two to three days before menstruation and continuing during two or three days of the flow.

She had been married on September 5. She presented herself on November 16 with pain in the right lower quadrant, vomiting, and urinary retention. The last menstruation was Oct. 7, 1955, after an interval of only 37 days. The previous interval had been about 7 weeks. On November 6, the thirty-first day of the present cycle, symptoms had begun. The patient was hopeful of pregnancy. The breasts were a little swollen and tender (not

\*In patients with great sensitivity to pregnandiol, the skin test often reaches a maximum in 48 hours or later, rather than in 24 hours. Likewise, in rabbits and guinea pigs which were made allergic to the steroid, the more severe skin reactions reached a maximum in 48 hours, while the moderate ones were greatest at 24 hours.

usual during her episodes of pain, etc.) but pelvic examination showed only extreme tenderness of the uterus and right appendage, a usual finding while she was having symptoms. Skin tests were given intracutaneously rather than subcutaneously. One to two micrograms of the steroid metabolites estrone, etiocholanolone, pregnandiol, pregnanediol, and pregnanetriol were given in 0.01 to 0.02 ml. plus a control of the aqueous suspending medium alone. This medium was Evans' solution, widely used by allergists as a vehicle for their test materials. Within five minutes a wheal appeared at the site of injection of pregnandiol. As the wheal developed, the patient's symptoms became more severe. Pain became incapacitating and she began to have retching. There was no reaction to the other steroids or to the control. Fifteen minutes after the initial tests, when the reaction to pregnandiol was reaching a maximum, a second identical injection of pregnandiol was given about 15 cm. from the first. There was no reaction to this test. (The possible significance of this will be discussed below.)

Five days later, tests were again carried out, this time with estrone and pregnandiol. The patient was still having severe symptoms and again the reaction to pregnandiol began within five minutes with aggravation of symptoms as the wheal developed. There was no reaction to estrone. On November 28, the twenty-sixth day of symptoms, there was slight vaginal bleeding, after which the symptoms began to subside. There was further spotting on December 4 and 5, the thirty-second and thirty-third days, by which time there was only occasional right lower quadrant pain.

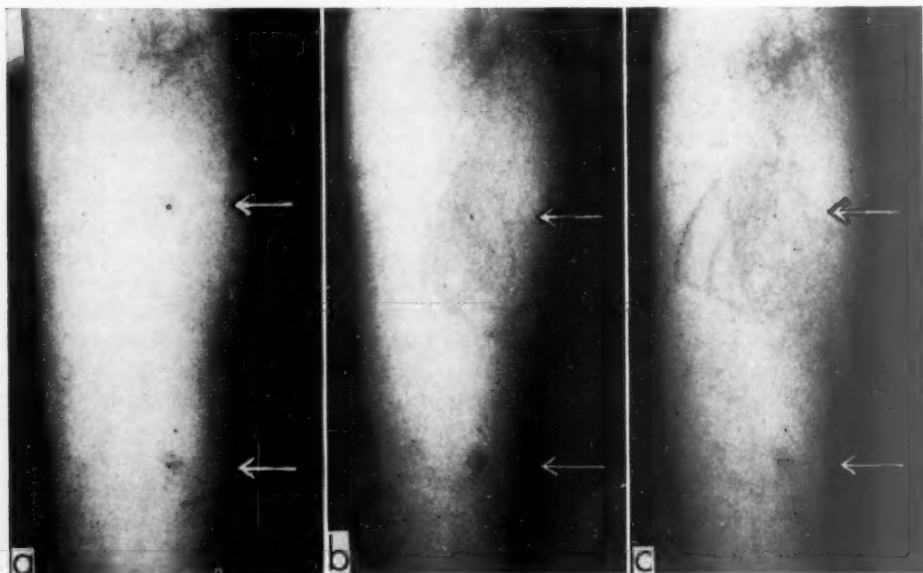


Fig. 1.—Reactions to 0.1 to 0.2 mcg. of pregnandiol and control given intracutaneously when the patient had been without symptoms for a month, Dec. 29, 1955, in the tenth week of pregnancy; pregnandiol above, Evans' solution below.

a, Photograph at 17 minutes; negative reactions to both pregnandiol and control.

b, At 24 minutes reaction to pregnandiol has begun.

c, At 32 minutes after injection maximum reaction to pregnandiol has developed. Note pseudopodia in both b and c. The patient developed right lower quadrant pain and retching as the skin reaction progressed.

On December 7, she felt well except for morning nausea typical of pregnancy. Examination showed slight enlargement and softening of the uterus. There was tenderness only in the region of the right ovary. Skin tests were repeated with the steroid hormone metabolites in the same amount and dilution as on November 16. The now familiar reaction to pregnandiol appeared a little later, at about 10 minutes rather than under 5 minutes as it had when she was having symptoms. There was no reaction to the other steroids. Fifteen minutes after the tests, when the wheal had reached a maximum, a second injection

of pregnandiol was given about 15 cm. from the first. There was only a slight reaction to this. The patient began to have pain and nausea during the development of the wheal. At 20 minutes, she was incapacitated with pain in the right lower quadrant and vomiting. Sufficient relief was obtained with morphine 0.016 Gm. so that she could return home. Pain continued for about 24 hours.

When the patient had been without severe symptoms for 4 weeks, passive transfer tests were carried out to see if any antibody to pregnandiol could be demonstrated in her blood serum. The serum was injected into the skin of five men. Twenty-four hours later pregnandiol was injected in the same areas as well as in control sites. All of the tests were negative immediately and at 24 and 48 hours.

Evaluation of the significance of the failure of passive transfer required that skin tests be repeated. The patient was therefore tested on December 29 to see whether allergy could still be demonstrated. Pregnandiol was given as before plus a control of Evans' solution alone. Both tests were negative in 17 minutes (Fig. 1, a). Shortly afterward, however, the reaction began. Photographs taken at 22 minutes and 34 minutes are shown in Fig. 1, b and c. As the reaction developed, the patient, who was feeling perfectly well when the tests were made, began to have severe pain in the right lower quadrant, nausea, and retching. The symptoms became incapacitating.

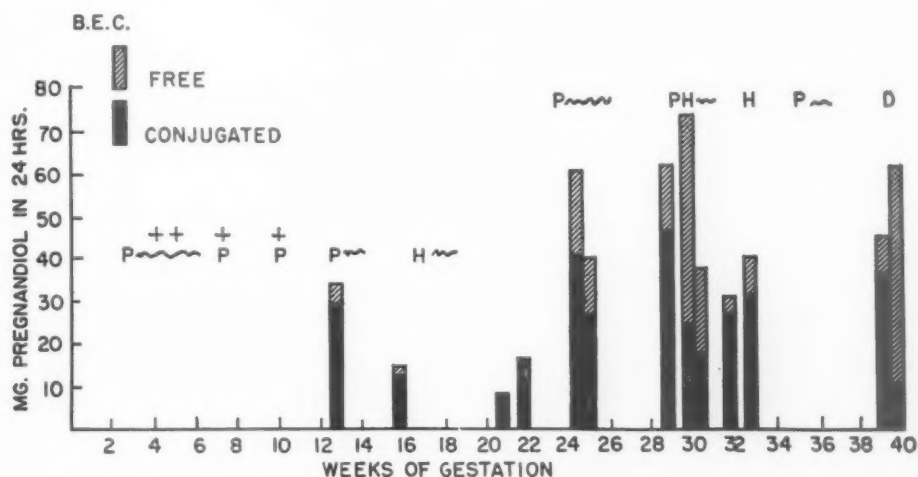


Fig. 2.—Excretion of pregnandiol during pregnancy in Patient B. E. C., allergic to pregnandiol. Total amounts of pregnandiol excreted in 24 hours are shown by the height of the columns. The relative amounts of free and conjugated steroid are indicated by the different shading, conjugated below, free above. Occurrence of symptoms is also shown.

P, Pain in right lower quadrant accompanied by vomiting and retention of urine.

PH, Duration of symptoms.

+, Skin tests performed.

D, Delivery of 4,300 gram girl.

H, Severe headache.

Pain and vomiting in the eighth and tenth weeks resulted from the skin tests and lasted only about 12 hours. The tests at 4 and 5 weeks aggravated the symptoms.

Assays are more widely separated than would appear because of necessary shortening of the horizontal axis (weeks of gestation). The last two assays, for example, are 3 days apart.

Delivery of the allergic patient fortuitously occurred at the end of a 24 hour period of collection of urine.

As a means of investigating allergy to pregnandiol it was desirable to measure the amount of the steroid excreted by patients allergic to it, both while they were having symptoms and when they were well, and to determine its state of conjugation with glucuronic acid. The assay of pregnandiol is technically difficult during the menstrual cycle because the amounts are small. During pregnancy, the excretion increases many fold so that assay is more practicable. Fortunately this patient was pregnant.

Twenty-four specimens of urine were collected at the times shown in Table I. Fig. 2 shows graphically the amounts of pregnandiol excreted and the proportions conjugated and unconjugated. It also indicates the occurrence of symptoms and the time of the skin testing described above. Because of the irregular cycle, calculations of the duration of pregnancy in the usual way, with delivery expected 280 days after the onset of the last menstrual period, would be meaningless. Fig. 2 was constructed by counting back from the date of delivery. The first day by this calculation becomes October 20. Her symptoms began on the eighteenth day, November 6, the probable date of ovulation. Delivery occurred on the two hundred and sixty-third day after this event.

### Method of Collection and Assay of Urine

During the 24 hour periods of collection, the patient put the urine as it was passed into a bottle containing 200 ml. of redistilled toluene. Extraction of free steroid was completed within a few hours after the final collection by shaking and separating the fractions. The toluene fraction containing the unconjugated pregnandiol was set aside. Part of the aqueous urine, 100 to 500 ml., was hydrolyzed with beta glucuronidase (Ketodase), freeing the conjugated pregnandiol which was then extracted with toluene. Purification of both toluene fractions was now carried out separately. The method of Goldfine and Cohen<sup>6</sup> was used for these procedures. The method of Talbot and associates<sup>7</sup> was used for colorimetric assay of pregnandiol. Color was developed with concentrated sulfuric acid. A Coleman Junior colorimeter was used with wave length set at 420 $\mu$ .

TABLE I. EXCRETION OF CONJUGATED AND UNCONJUGATED PREGNANDIOL DURING PREGNANCY OF PATIENT B. E. C., ALLERGIC TO IT

DATE, 1956	WEEK OF PREG-NANCY	PREGNANDIOL EXCRETED				CONDITION OF PATIENT
		TOTAL (MG./24 HR.)	CONJUGATED (MG./24 HR.)	FREE (MG./24 HR.)	% UNCONJUGATED	
January 20-21	13	34.7	30.2	4.5	13.0	Severe symptoms
February 7-8	16	14.7	13.2	1.5	10.2	Well
March 14-15	21	8.5	8.3	0.2	2.4	Well
March 21-22	22	16.6	16.1	0.5	3.0	Well
April 9-10	25	61.2	41.5	19.7	32.2	Severe symptoms
April 12-13	25	40.5	27.5	13.0	32.1	Severe symptoms
May 9-10	29	62.2	47.2	15.0	24.1	Well
May 16-17	30	74.3	25.1	49.2	66.2	Severe symptoms
May 20-21	31	37.3	18.0	19.3	51.7	Severe symptoms
May 30-31	32	31.4	27.9	3.5	11.1	Well
June 7-8	33	40.6	32.0	8.6	21.2	Headache
July 22-23	40	55.2	47.0	8.2	14.9	Well
July 26-27	40	62.0	21.0	41.0	66.1	Labor during last 6 hours of collection with delivery at end of 24 hour interval

Identification and purity of the crystalline precipitates of both conjugated and unconjugated fractions of May 16-17 were established by spectrophotometry.



The absorption curves obtained in concentrated sulfuric acid on a Beckman DU spectrophotometer corresponded almost exactly with that of pure 3 alpha, 20 alpha pregnandiol.

On Jan. 19, 1956, the patient again began to have constant pain and vomiting which continued until January 31, the thirteenth to the fifteenth weeks. Thirteen per cent of the pregnandiol excreted during the 24 hours, January 20 to 21, was in the free form. February 7 to 8, when she was again well with only occasional mild pain, 10 per cent of the pregnandiol was unconjugated, and on March 14-15 and 21-22, the percentages were only 2 per cent and 3 per cent, respectively. Total amounts of pregnandiol excreted were also relatively smaller when the patient was well.

She had severe symptoms at roughly cyclic intervals lasting about 12 days until 4 weeks before delivery. At the end of the seventeenth week, severe frontal headache occurred (exactly 4 weeks after the onset of the previous episode of pain). It lasted about 12 days. The episode of pain and vomiting in the thirtieth week was accompanied by similar headache. Headache lasting only 2 days occurred in the thirty-third week when 21 per cent of the pregnandiol was unconjugated (see Fig. 2 and Table I).

With the episodes of pain at 24, 30, and 35 weeks, it was thought that delivery was imminent. Severe cramps localized in the right lower quadrant were accompanied by uterine contractions and there was vomiting, inability to empty the bladder, and headache. During the episode of pain at 30 weeks the largest excretion of pregnandiol was observed, 74 mg. in 24 hours, 66 per cent of it unconjugated. There was no albuminuria or evidence of urinary infection. Total serum protein was 5.6 Gm. per cent, albumin 3.2, globulin 2.4. Since impaired liver function might be surmised in view of the large amount of unconjugated steroid, liver function tests were obtained. Cephalin flocculation was negative, thymol turbidity was 8 units. At 33 weeks, when the patient was again relatively free of symptoms, cephalin flocculation was negative and thymol turbidity was 4 units.

At 35 weeks severe symptoms occurred again. This time the urine was infected and no assays for pregnandiol were done. After 10 days the symptoms cleared.

The patient had a remarkably easy and uneventful labor with spontaneous delivery of a 4,300 gram girl. She says that in retrospect there was no difference between the pain of labor and that which she experienced in the twenty-fourth, thirtieth, and thirty-fifth weeks. The pain of labor was largely on the right side. Indeed, it was easier to bear because now she wanted the baby to be born, and an end to her discomfort was in sight.

The 24 hour urine specimen saved 5 days before delivery when the patient was well proved to contain 55 mg. of pregnandiol, 15 per cent of it in the free form. Fortunately, she had begun to save the last 24 hour specimen almost exactly 24 hours before her delivery. Labor began at about 1:00 A.M. on July 27, 1956, and she was delivered at 7:00 A.M. The last of the urine specimen was obtained by catheterization a few minutes before delivery. This specimen contained 62 mg. of pregnandiol, 66 per cent of it unconjugated.

TABLE II. EXCRETION OF CONJUGATED AND UNCONJUGATED PREGNANDIOL BY NORMAL PREGNANT WOMAN E. T.

DATE, 1956	WEEK OF PREGNANCY	PREGNANDIOL EXCRETED			
		TOTAL (MG./24 HR.)	CONJUGATED (MG./24 HR.)	FREE (MG./24 HR.)	% UNCON- JUGATED
February 29-March 1	16	22.3	22.3	0	0
March 14-15	18	3.2	3.1	0.07	2.3
March 21-22	19	8.4	7.8	0.53	6.3
March 28-29	20	13.0	13.0	0	0
April 11-12	22	8.8	8.5	0.27	3.1
April 25-26	24	4.8	4.7	0.08	1.6
May 10-11	26	15.9	15.8	0.09	0.6
May 22-23	27	13.7	13.2	0.47	3.4
June 7-8	30	15.9	15.8	0.06	0.04



Coincident with the assays of urine from the patient B. E. C., urine from a normal 30-year-old woman in her fourth pregnancy was collected and assayed under the same conditions. The results are shown in Table II. The largest total excretion was recorded in the sixteenth week, none of it unconjugated. In the nineteenth week 6 per cent of a total of 8.4 mg. was unconjugated. No unusual symptoms were recorded at this time of relative highest excretion of unconjugated pregnandiol.

### Comment

It is not assumed that the excretion of relatively large amounts of unconjugated pregnandiol is necessarily abnormal. It has been supposed that most, if not all, is excreted in conjugated form, but there is no proof of this.<sup>1</sup> An increase in unconjugated steroids at the time of labor may be normal, for free estriol and estrone have been observed in the urine at that time.<sup>8, 9, 10</sup> It is possible that there is normally a cyclic fluctuation in the relative amount of free pregnandiol like that observed in the patient B. E. C. Heckel<sup>11</sup> reported the assay of pregnandiol throughout pregnancy in a number of normal pregnant women by a method which measured the glucuronic acid after hydrolysis following the extraction of pregnandiol glucuronide. A roughly cyclic rise and fall were noted in all cases. Since there was no measure of unconjugated pregnandiol by the method of assay, apparent cyclic decreases may have been due to increases in the relative amount of unconjugated pregnandiol.

Whether or not the amounts of unconjugated pregnandiol excreted by patient B. E. C. are abnormal, her sensitivity to the steroid is of critical importance. A number of questions arise, the answers to which must at present be speculative.

Why would less than a microgram of pregnandiol injected into the skin produce such profound reactions when at the same time the patient was probably excreting some milligrams of free pregnandiol in the urine during a 24 hour period? The amount of pregnandiol in the blood at any one time was probably extremely small. Further, the pain and vomiting resulting from the skin tests in this case are analogous to the known immediate occurrence of a severe attack of asthma incident to skin test in certain highly sensitive patients allergic to pollen. It is probably not that the pollen gets into the blood and affects the shock organs directly. It is rather that the sensitive autonomic nervous system overreacts according to an established pattern.

If the relatively high levels of unconjugated pregnandiol and the occurrence of severe symptoms represent cause and effect, how could the patient be well when she was excreting more than 20 per cent unconjugated, as she did during the twenty-ninth week, and why did she not have vomiting and retention of urine during the 24 hours preceding labor when 66 per cent of the pregnandiol was in the free form?

It is possible that, had she not been delivered, the other symptoms would soon have appeared. Relatively large amounts of unconjugated pregnandiol may precede the onset of symptoms. When 24 per cent was unconjugated

\*It has been reported that etiocholanolone, a metabolite of testosterone normally excreted in the urine, consistently produces fever and other systemic effects when injected intramuscularly in man.<sup>14</sup>

without symptoms in the twenty-ninth week, the amount of unconjugated pregnandiol may have been increasing, for symptoms began 4 days later, and 6 days later when the next assay was made, 66 per cent was in the free form.

The degree of sensitivity of the patient or, more specifically, the state of reactivity of her autonomic nervous system varied. That the sensitivity of the skin varied is indicated by the delay in the reaction of the skin to pregnandiol when the patient was relatively asymptomatic compared to the time of reaction when she was having severe symptoms. When the first two skin tests were made, she was having severe symptoms; the autonomic nervous system was in a sensitive state so that the local reaction occurred rapidly. With the third test, 5 days after the cessation of severe symptoms, the local reaction occurred a little later. When the fourth test was made, she had been well for a month and the time between the giving of the test and the beginning of the reaction was several times that of the first two tests.

The autonomic nervous system appears to have a limited reserve of reactivity. This is manifested in the phenomenon familiar to allergists as *alternation of shock organs*. A patient subject to both asthma and allergic rhinitis may suffer from either one, but he is not likely to have both at once. If he should undergo an attack of hives, he may have neither asthma nor hay fever during the attack.\* At the time of labor the autonomic nervous system became involved in labor. This may have precluded other reactions which would ordinarily result in vomiting, urinary retention, etc.

The apparent local exhaustion of the reacting mechanism, twice observed in this patient, may be a phenomenon similar or related to alternation of shock organs. On November 16 and again on December 7, an identical injection of pregnandiol was given on the same forearm when the initial reaction had reached a maximum. The second test failed completely to react on November 16 and reacted only mildly on December 7.

It has been pointed out that symptoms associated with allergy to pregnandiol often begin after a pregnancy.<sup>4</sup> In view of the large amounts of free steroid excreted by this patient and the finding that the normal pregnant patient also excreted unconjugated pregnandiol, it may be postulated that susceptible women become sensitized at times when free pregnandiol is present. Similarly, a sufferer from allergy to some exogenous substance becomes sensitized at some exposure to it, not necessarily the first. His sensitization may coincide with exposure to a particularly large amount of the allergen. In women whose symptoms begin after a pregnancy, the onset follows delivery by a few months. It usually coincides with the first ovulatory cycle, that is, with the first reappearance of pregnandiol. These women often recall that their symptoms began premenstrually. In some cases the onset was so sudden and dramatic that years later the patient's recollection of it is remarkably vivid and concise.

\*Remission or marked improvement of asthma and allergic rhinitis may follow an attack of angioneurotic edema, and at times improvement follows major surgery. The reaction of the autonomic nervous system appears to undergo some reorganization as a result of the shocking episode. This may explain the temporary improvement of some patients with ovarian pain after traumatic procedures such as intrauterine cautery<sup>12</sup> or pelvic operations such as uterine suspension, which is frequently done if the uterus happens to be retroverted. Similarly, temporary remission may follow the removal of the painful ovary, but subsequent pain, most often in the remaining ovary, and other symptoms are usually more severe when they return in a few months.<sup>13</sup>

### Summary

A patient allergic to pregnandiol was studied during a pregnancy when symptoms of ovarian pain, vomiting, and urinary retention similar to those she had previously experienced premenstrually continued to recur cyclically.

Extreme skin sensitivity to pregnandiol was demonstrated on four occasions, two when she was having severe symptoms and two when she was well. When she was having symptoms, the reaction to 0.1 to 0.2 meg. of 3 alpha, 20 alpha pregnandiol given intracutaneously developed within 5 minutes and the symptoms were aggravated. When she was well, the wheal developed in 10 to 20 minutes and identical symptoms were produced. Thirteen 24 hour urine specimens were assayed for both free and conjugated pregnandiol. In five specimens obtained when the patient was having severe symptoms, 13 per cent to 66 per cent of the pregnandiol was unconjugated. In seven specimens obtained when she was well, 2 per cent to 24 per cent was in the free form. During the 24 hours before delivery, when there were no symptoms other than those normally associated with labor, 66 per cent of the pregnandiol was unconjugated.

Assay of nine 24 hour specimens of urine from a normal pregnant woman showed 0 to 6 per cent of the pregnandiol unconjugated.

It is postulated that conjugation of pregnandiol with glucuronic acid is a protective mechanism and that the free steroid is responsible both for the inception of allergy to pregnandiol in susceptible women and for the later cyclic recurrence of symptoms.

We wish to thank Dr. Henry Scherp, Dr. Anthony Izzo, and Dr. William Strain for technical aid and encouragement. We are indebted to Parke, Davis & Company for the supply of 3 alpha, 20 alpha pregnandiol, and to Warner-Chilcott Laboratories for the Ketodase used in the extractions. We are most grateful for the selfless cooperation of the patients B. E. C. and E. T., and for aid in the passive transfer study by Dr. Stearns Bullen, Sr., Dr. George Dean, Dr. Leonard Horn, Dr. Robert Todd, and Dr. Charles Warren (deceased).

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## ABDOMINOVAGINAL ELECTRIC POTENTIAL DIFFERENCES WITH SPECIAL REFERENCE TO THE OVULATORY PHASE OF THE MENSTRUAL CYCLE\*

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THE generation of minute electric potentials is a property of the surface of all living tissues. By sensitive electrometric measurement it should be possible therefore to depict specific potential activity associated with physiological changes accompanying ovulation. To date investigations directed toward measuring significant potential differences have been inconclusive in denoting clearly the day of ovulation.<sup>2, 6-9</sup> In an investigation of electropotential changes with neoplastic disease of the genital tract differences were noted in the vaginal potential between menstruating and postmenopausal women.<sup>13</sup> It is our purpose to report promising results of electropotential studies employing a revised technique and a more highly sensitive recording apparatus, in which a midcycle alteration of potential is seen with predictable regularity. These observations are absent in the menopausal individual.

### Review and Comparison of Electrometric Systems

The major points by which these studies differ from those previously undertaken are (1) the type of electrode employed and (2) the sensitivity of the recording apparatus.

#### *Electrodes.—*

The previous investigators working on this problem almost universally employed silver-silver chloride electrodes. In one of the earliest studies on electropotential measurement Langman and Burr<sup>1</sup> used a microvoltmeter, a recording galvanometer, and silver-silver chloride electrodes. One electrode was strapped on the lower abdomen above the symphysis pubis while the other was placed at or alongside the cervix.

Max, Mauss, Day, and Rhoads<sup>3</sup> likewise employed silver-silver chloride electrodes. Fine silver rods, cylindrical in shape, 25 cm. long and 3 mm. in diameter, were used as probing electrodes and a flat 3 by 4 cm. rectangular silver plate was used as the indifferent or reference electrode. An even coating of silver chloride was electroplated onto both types of electrode prior to use. The electrodes had to be inspected after each operation to be sure that no break had occurred in the friable silver coating. When breaks were found the electrode had to be sanded down to the silver and replated.

\*These studies, which were carried on in the laboratories of the Lemuel Shattuck Hospital (Massachusetts Department of Public Health), have been supported by research grants from the U. S. Public Health Service, U. S. Department of Health, Education and Welfare.



Rock and associates,<sup>2</sup> in measuring skin potentials, employed a large silver-silver chloride plate about 45 sq. cm. in area for the reference electrode. This was fastened just above the knee by means of a loose elastic binder. A layer of cotton soaked in physiological salt solution was placed between the silver chloride sheet and the skin. The silver-silver chloride exploring electrode with an effective area of 16 sq. mm. also had a small piece of cotton moistened in physiological saline interposed between it and the actual point of contact on the skin. Silver-silver chloride electrodes have been shown to be sensitive to hydrogen and chloride ion concentration and hence may generate diffusion potentials which interfere with biological records.

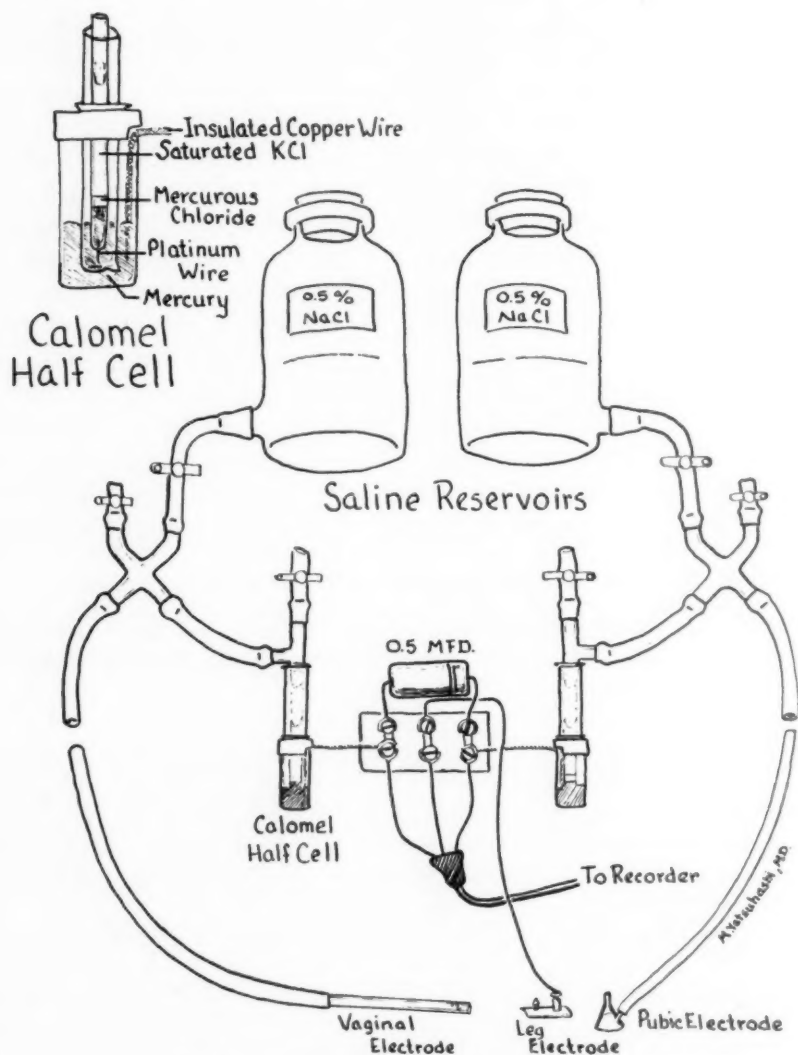


Fig. 1.—Schema of calomel electrode system.

In this present study the vaginal-cervical potentials are measured instead by glass rod electrodes (3 mm. inner diameter and 8 inches in length) by the method previously described by Katzka, Lemon, and Jackson.<sup>5</sup> The exploring electrode is connected to a calomel half-cell unit by a tube with a minimum 6



mm. inner diameter filled with physiological saline (Fig. 1). A piece of sterile cotton partially inserted into the distal end of the glass rod allows flushing of saline through the electrode but prevents escape of saline and entrance of air. A similar tube filled with saline passes from the calomel half-cell unit to a glass funnel placed in contact with the skin of the pubis. In previous studies it was found that the rubber tubing of smaller caliber failed to give adequate recording of potential change. When the glass rod is against the vaginal-cervical epithelium and the other electrode is in place on the skin above the symphysis, the electrical circuit is completed by the tissue and extracellular fluid between the mucosa and the pubic skin. A third lead (metal) is attached to the leg, grounding the patient. In this manner extraneous potentials are eliminated. No attempt will be made to describe the calomel half-cell unit, for it has been adequately described by others.

This type of liquid-junction electrode was chosen, for it most clearly followed the criteria for the ideal electrode set up by the experimental studies of Kennedy and Travis.<sup>4</sup>

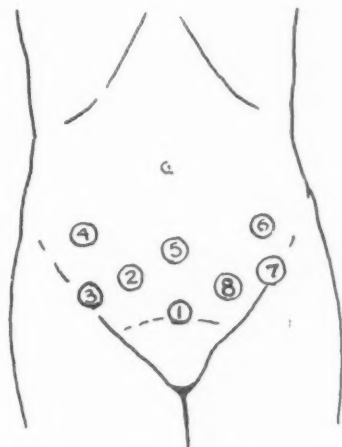


Fig. 2.—Sites of abdominal-vaginal recordings taken to determine surface electropotential gradients.

Rock and his co-workers,<sup>2</sup> using the large silver-silver chloride plate previously described, found great difficulty in locating properly on the skin surface a reference electrode which would be stable in potential. They commented that potential foci could be observed at almost any point on the abdomen and that there was no demonstrable connection with the underlying organs. Kennedy and Travis,<sup>4</sup> however, found that the effect of skin movement was to raise the rigid metal electrodes from the skin surface, thus changing suddenly the surface area in contact with the electrode. This sudden change in surface area produced an increased resistance which tended to block the flow of electrons and introduced artifacts into the record. They found that this factor disappeared completely when fluid-filled electrodes were employed.

To confirm this observation of Kennedy and Travis, we placed our glass liquid-junction skin-surface electrodes at the sites numbered in Fig. 2 with the vaginal electrode in contact with the cervix to complete the electrical circuit. The recording of each site was done on the graph, alternating the recording by removing the input jack on the machine to start a new test or by removing the surface electrode only without breaking the electrical contact of the half cells and the recording machine.

At each site the potential varied less than 5 mv. The majority registered the same or 1 to 2 mv. difference.

By using the glass electrodes we have been able to maintain electrolytic contact with negligible resistance for indefinite periods of time. The number of artifacts that may arise from diffusion potential gradients, bodily movement, vibration, or skin irregularity have been materially reduced. The glass electrodes are easy to apply and remove and are well tolerated by the patients for long periods of time. They are readily sterilized by boiling after each application and have proved extremely durable. The tedious process of replating the friable silver coating on the silver-silver chloride electrodes is avoided and the necessity of accurate matching of pairs of silver-silver chloride electrodes has been obviated.

#### *Recording.—*

We believe the recording device used in this electropotential study to be far more sensitive than the instruments previously employed in this work.

Max, Mauss, Day, and Rhoads,<sup>3</sup> used a decade potentiometer circuit of traditional form with a potential range of 10  $\mu$ v to 1 v. A galvanometer with a constant impedance shunt designed to give critical damping was used, permitting a completion of reading in 10 to 40 seconds.

Rock and associates employed a Leeds Northrup Type R galvanometer which uses the null indicating method. The effective input resistance to the measuring circuit was 2 megohms. The null point was usually quite sharp and currents less than  $5 \times 10^{-10}$  amp. flowed in the electrical circuit. The unbalanced potential was shunted by a vibrating contact at the grid of the first tube of a high gain audiofrequency amplifier. Fairly accurate potential determinations could be made in 3 to 5 seconds. To accomplish this, however, it is necessary to anticipate the deflection of the galvanometer by rapid manipulation of the potentiometer to keep the deflection at the zero point.

The ideal measuring instrument, as noted by Ravin and co-workers,<sup>12</sup> "should have a relatively high electrical resistance compared with the resistance of the electrode in order that voltage readings at the instrument be a close approximation of that at the tissue. With high resistance in the galvanometer, virtually no current will be drawn from the tissues which would decrease tissue potential."

The recording instrument we now use was originally designed by Sanborn Company, Cambridge, Massachusetts, for Lemon and his co-workers for studies of the potential variables in the gastric mucosa. Its basic design has been reported elsewhere. This recording galvanometer uses many components of a Twin-Viso direct writing electrocardiograph. It most clearly fits the requirements for the ideal recording device and is commercially available.

This millipotentiometer has a 5,000 megohms impedance which prevents current flow through the circuit. The sensitivity of the instrument and the stability of recording are such that once the machine has been balanced (the writing stylus set at zero) no further manipulations are necessary. Mechanical artifacts are eliminated from the records. Thus, it is possible to record for as long an interval as necessary. The usual interval covers a 15 to 25 minute span.

The over-all sensitivity of the instrument can be raised to a level of 1 cm. deflection for an input of 5 mv. We have adjusted the sensitivity so that a 1 mm. deflection of the writing stylus corresponds to a 1 mv. input. There are variable recording speeds. We have used a rate of 3 cm. per minute. Two recording channels may be employed simultaneously, if desired.

The recording paper is divided into two sections. Each section consists of 5 cm., further subdivided into 0.1 cm. so that values of 50 mv. can be recorded. The base line of zero is arbitrarily placed at the midpoint of the paper

so that values of plus 25 to minus 25 mv. are recorded. Dial controls enable the base line to be moved in either direction for values greater than plus 25 or minus 25 mv.

### Method

The recording galvanometer is switched on 30 minutes preceding the test to allow the circuits and vacuum tubes to stabilize. Before each test the recorder is balanced, that is, the sensitivity adjusted to 1 mv. deflection and the writing stylus set to the center of the recorder paper, setting the base line as 0 potential or, as previously discussed, plus 25 or minus 25 mv.

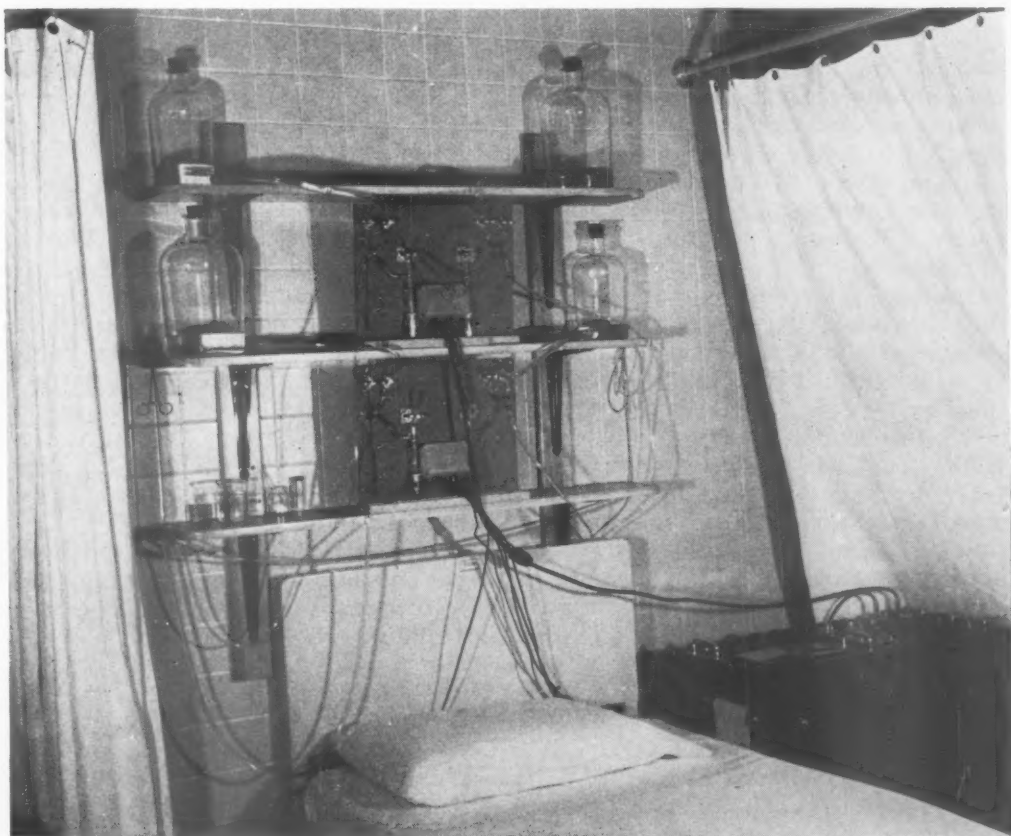


Fig. 3.—Mounted calomel half cells and Sanborn Twin-Viso recorder.

The patient assumes a prone position upon the bed. Two glass funnel electrodes are strapped on the right dorsal forearm by means of perforated rubber bands, completing one circuit. A similar band is placed around the abdomen holding another glass funnel in place on the pubic symphysis. The electrodes are then flushed with normal saline from the reservoirs to insure good liquid junction. It is most important that bubbles be absent from any point in the system. To complete the second circuit the probing electrode is then filled with physiological saline and inserted by inspection into the vagina with slight pressure until contact is made with the mucosa of the cervix or left vault and then flushed with saline to eliminate any air bubbles which might have entered during insertion. The ground leads of both circuits are attached to the leg with the use of electrode jelly as a conductor. A rectal thermometer

is inserted into the rectum as a temperature control. Contact to the recorder is made via input jacks which are plugged into the direct current amplifier and a recording is taken for 15 to 25 minutes.

On completion of the electropotential recording the following additional tests are made: (a) vaginal pH, (b) fern crystallization on the vaginal mucus, (c) a Papanicolaou smear, (d) glycogen determination smear, (e) rectal temperature.

None of these tests has proved consistent for all patients under all conditions.

### Results

A series of 44 women have been studied.

Extensive testing has been possible, for these patients have been hospitalized at the Lemuel Shattuck Hospital for Chronic Diseases (Massachusetts Department of Public Health). The length of hospitalization has usually been prolonged. On discharge from the hospital its accessible location has made it possible to continue tests on an outpatient basis.

The ages of the patients varied from 18 to 88 years. Physiologically these patients have been grouped either as premenopausal, menopausal, or postmenopausal. Wherever possible, daily readings were taken and sufficient numbers of tests were run (1) to establish their physiological grouping, (2) to eliminate extraneous interference from medications, etc., (3) to establish dating of ovulation if cyclic activity is recorded. To determine the normal base line for each patient, readings are taken during the menses and for 7 days thereafter. Little or no potential difference is recorded in the voltage at the time of menstruation.

Interpretations of the readings obtained are based upon (1) the initial voltage, (2) the increased or final level of voltage attained, and (3) the time taken to reach the final level. It is the slope of the curve that seems to be most important in establishing a cyclic rhythm in these curves.

The *initial voltage* will vary depending on the physiological group of the patient as well as the phase of the menstrual cycle at the time the tests are made. Variations of initial voltage up to 10 mv. from the norm have been noted in each phase in some individuals (Table I).

TABLE I. COMPOSITE RESULTS OF TEN NORMAL PREMENOPAUSAL MENSTRUAL CYCLES

INITIAL POTENTIAL SHIFT	CURVE	FLUCTUATION	DAY OF CYCLE	ENDOMETRIAL BIOPSY
Negative Minus 18 mv.	Very small rise	Small 10 to 15 mv.	1 to 10	Menstrual
Negative Minus 25 to minus 20 mv.	Very sharp rise	Large 35 to 50 mv.	13	Proliferative
Less negative or positive Minus 5 to plus 10 mv.	Small rise with flatten- ing	Small 10 mv.	14	Early secretory
Negative Minus 20 to minus 25 mv.	Very sharp rise	Large 35 to 50 mv.	16	Secretory
Negative 20 mv.	Small rise Almost flat curve	Very small 5 to 10 mv.	18 to 28	Secretory

The increase in potential from the initial voltage and the time taken to attain the level permits us to make some observations on the cyclic activity for the different physiological groups.



*A. Normal Premenopausal Readings.*—Following menstruation normal women show successive daily changes in their initial electropotential differences and the type of the restoration curve. These results have been *reproducible* from patient to patient and from the day of one cycle to the corresponding day of the next cycle or a reading taken in a later cycle.

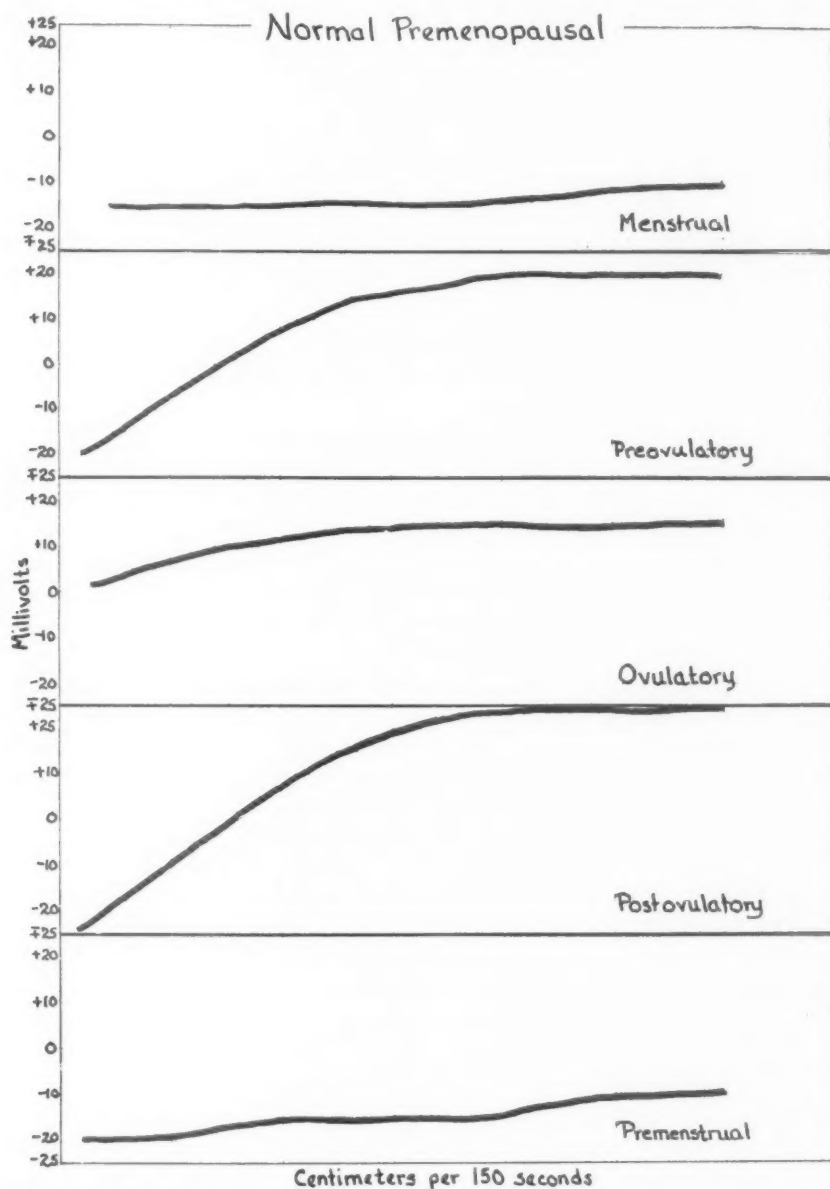


Fig. 4.—Typical curves recorded at labeled stages of a normal menstrual cycle.

The characteristics of these curves are as follows:

*A. Premenstrual* curves are relatively flat with negative origins of minus 20 mv. and final readings of minus 10 to minus 4 mv. The slope of the curve tends to increase slightly on successive days as the menstrual period approaches (Table I).



B. *Menstruation* is associated with little or no potential differences. Voltages are maintained in negative ranges from minus 20 to minus 8 mv. A flat curve is noted. Each patient appears to have an individual base line level at this point.

C. Approaching the midportion of the cycle during a period of 24 to 48 hours, a steep positive increase is noted. The curve rises from minus 20 to plus 20 or 30 mv. in 10 to 15 minutes.

D. At the midcycle an abrupt change in potential develops. This is consistently marked by electropotential difference curves which are usually positive in origin, plus 8 to plus 20 mv. The curve remains flat with sustained readings of plus 12 to plus 22 mv. for intervals of 10 to 15 minutes. This type of curve persists for 1 to 2 days. It is at this point that we believe ovulation occurs.

E. Following this, subsequent curves resemble those of the immediately preceding phase with extreme negative potentials rising in 10 to 15 minutes to plus 25 or 30 mv. (Table I).

The numerical values of the days of the cycle may vary according to its length but the flat positive potential after a preliminary rise is constant in all normal premenopausal cycles.

B. *Menopausal Readings.*—Women in the menopausal stage of life present different electropotential readings from those seen in premenopausal women, not only in the time lapse from one phase of the cycle to another but also in the appearance of the curve. The curve is consistently flat with depressed voltage. These patients with irregular menstrual periods do not show a transition from one phase of the cycle to another. An abrupt change takes place from a flat negative postmenopausal reading to the flat late cycle premenstrual curve of positive voltage. The characteristic low negative initial shift followed by a sharply ascending curve to positive levels in the range of plus 25 to 30 mv. seen in the normal preovulatory phase (midcycle anomaly) is absent.

C. *Postmenopausal Readings.*—Postmenopausal women usually attain a reading of high positive voltage in the range of plus 40 to 60 mv. at the beginning of the test or shortly thereafter. A flat curve is the result. Although the maximum voltage varies in individuals (plus 10 mv.) the type of curve associated with postmenopausal physiology is very much like the curve found in patients who have had a surgical or radiation castration for carcinoma of the genital tract.

D. *Control Observations.*—The differences in potential previously noted could conceivably be due to artifacts in the recording machine or to some diffusion change in the saline electrode control. We offer the following control observations in support of the contention that these potential measurements are biologically valid:

1. The length of time of insertion of the probing electrode had no bearing on the readings. Moreover, after the completion of each test the circuit was broken and reinstated without any alteration in the potential change from the previous reading.
2. Flushing the vaginal electrode does not affect the potential.
3. The stability of the reference electrode has been established.
4. The readings do not vary with the position of the probing electrode in the vagina. It appears to make little difference whether the electrode is in contact with the cervix or the vaginal fornix.

5. Data compiled from 6 patients tested on a given day had readings consistent with their particular phase of the cycle regardless of the potential measured on the preceding patient.

### Comment

Vasomotor disturbances, minute variations in skin temperature, humidity, and focal changes in pH have all been used as probable explanations of the potential variations.<sup>6, 7</sup> Emotional unrest has been said to bring about local changes in the peripheral cutaneous blood flow due to alterations in capillary tone, as well as changes in skin resistance. Such changes produce focal differences in the pH which Rock<sup>2</sup> believes explains the variation in the electropotential readings. The saline electrodes used in this study are not affected by changes in pH from 1.0—8.0.<sup>5</sup>

Our present findings seem to indicate that in normal premenopausal women, temperature, pH, and potential are closely allied but not interdependent.

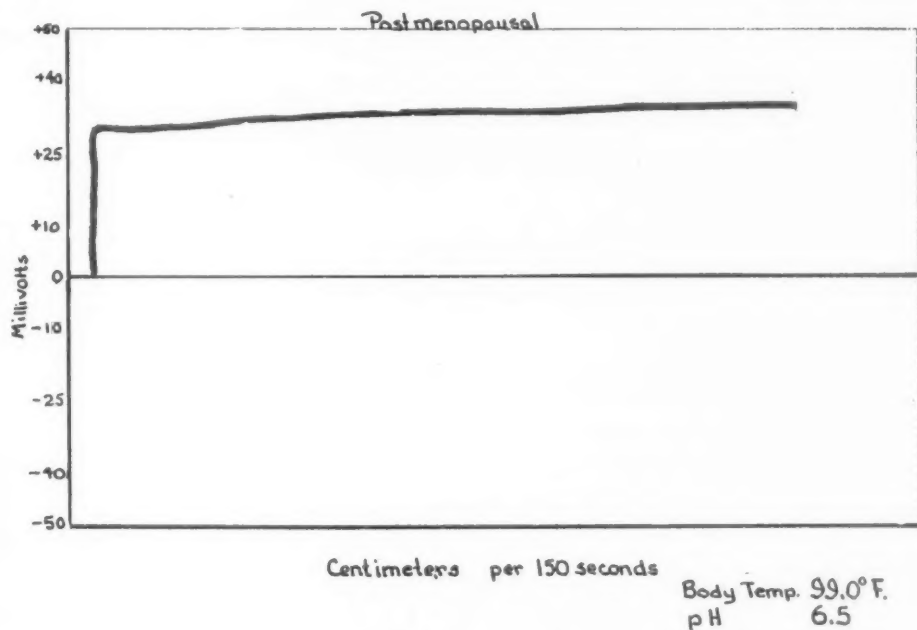


Fig. 5.—Graph of electropotential recording of a postmenopausal woman.

Cyclic changes in temperature and pH are clearly evident during the menses, prior to the preovulatory curve, after "ovulation," and again premenstrually. However, temperature and pH singly or in combination do not alter the potential readings in the postmenopausal group which maintain a high, flat voltage of plus 30 to plus 60 mv. without the sharp cyclic changes of premenopausal women with the same temperature and pH values.

Figs. 5 and 6 are given as examples. The pH 6.5 is usually correlated with menstruation and a negative value of minus 15 to minus 10 mv. of premenstrual women. Temperature 98.8° to 99° F. is a relatively constant temperature, not only for this patient but in both the pre- and postmenstrual phases when the curves are in negative voltage (Fig. 5). Burr<sup>10</sup> in his work makes the same observation.

Another instance (Fig. 6) is cited to illustrate further the independence of temperature, pH, and potential. A 31-year-old premenopausal patient with acute generalized psoriasis ran a temperature of 101° F. daily, yet her potential values remained negative in the extreme ranges of minus 30 to minus 50 mv. Her pH values were consistently 4.5 to 5.0. She did not show a rising curve at any time despite the high temperature and acid pH.

There can be little doubt that psychogenic factors influence potential but not enough to cause sustained readings of 25 to 30 mv. A distinguishing characteristic of the so-called "psychogenic" potential is the return to the base line reading after an initial rise or fall. It is not comparable to the sharp sustained increase in potential prior to what we believe is ovulation. There is a psychogenic factor of considerable magnitude brought out when the "excitable," apprehensive patient views the imposing calomel half-cell board for the first time. It was first felt that the high potential variants were due to this "nervous" psychogenic factor. As the work progressed and a clearer demarcation between physiological groups evolved, it became evident that the so-called nervous reactions recorded were actually repetitive readings which could be reproduced in a later cycle for the premenopausal group or daily in the postmenopausal group.

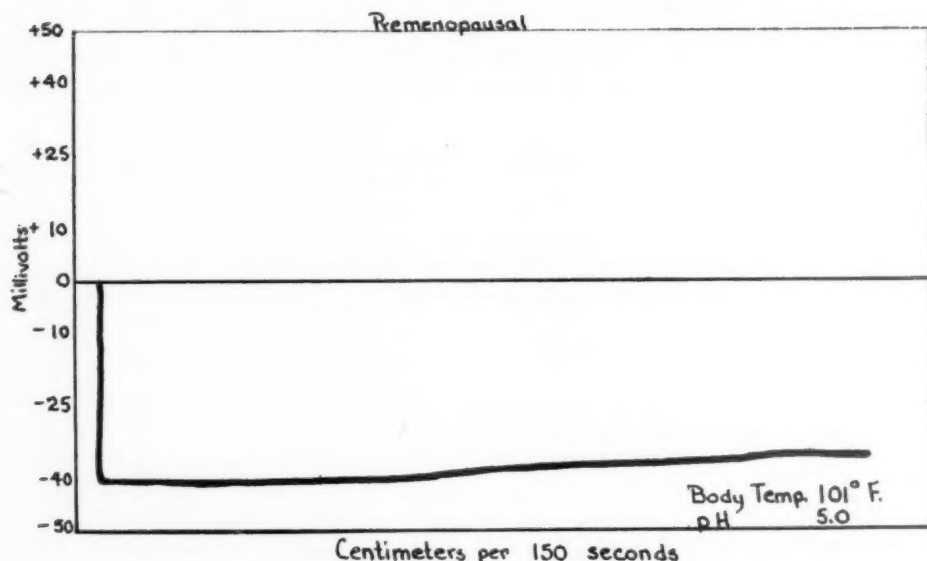


Fig. 6.—Graph of electropotential recording of a premenopausal patient showing contrasting voltage with relation to pH and temperature.

It appears that temperature, pH, and psychogenic factors influence the potential but do not give the repetitive and cyclic changes observed during the menstrual cycle in presumed association with periodic ovulation.

Other factors may influence the potential variations. As observed, drugs such as morphine and Nisentil produce a sharp increase in potential as compared with cortisone, which depresses the potential in proportion to the dosage given. The ramification of the pharmacological effect of different drugs has not yet been explored, but must be controlled in all further studies of this nature.

### Summary

1. The electropotential difference between the skin of the abdomen and the vagina can be measured consistently and accurately with a Sanborn Company Twin-Viso recording millipotentimeter using calomel half-cell liquid saline junction electrodes.

2. Premenopausal women exhibit cyclic changes in vaginal-cervical electropotentials compared to those of the skin of the abdomen.

3. Cyclic vaginal-cervical electropotentials have characteristic patterns, with a midcycle change not found in postmenopausal, irradiated, or surgically castrated women.

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## AGENESIS OF THE GONADS\*

### Case Report

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TURNER'S syndrome,<sup>1</sup> ovarian agenesis,<sup>2</sup> or Bonnevie-Ullrich syndrome<sup>3, 4</sup> has been variously reported in the world literature. Several reviews now place the number of cases at 117.<sup>2, 5, 6, 7</sup> The basic findings of short stature, sexual infantilism, high urinary gonadotropin levels, and agenesis of the gonads, often associated with other congenital defects, establish the diagnosis.

R. H., an 18-year-old white, single nullipara, was seen in the Out-patient Department of the Long Island Jewish Hospital with the chief complaint of lack of breast development, amenorrhea, and stunted growth. She had normal growth during childhood, but failed to have the usual adolescent change and development. She did not think herself unusual until she entered high school. There was no family history of growth abnormalities and there were no siblings. Scant pubic hair was noted at 14 years of age. Axillary hair never appeared.

Physical examination showed a short individual, 59 inches in height, with a webbed neck, permanent shield chest, and poor breast development with inverted nipples. Cubitus valgus was marked. The blood pressure in the upper extremities was 130/90; in the lower extremities 135/92. Axillary hair was absent; pubic hair was scant. The ratio of the trunk to the lower extremity, measured from the symphysis pubis, was normal. The external genitals were infantile, and the labia were agglutinated with only a small external opening present. The hymen was intact. Rectal examination disclosed a retrocessed hypoplastic uterus. No adnexa could be palpated.

Laboratory findings were as follows: Bone survey studies showed spina bifida, osteoporosis of the carpus, tarsus, and vertebrae, with delayed epiphyseal closure. There was no abnormality of the sella turcica. The protein-bound iodine was 9.8 mg. per cent. Fasting blood sugar was 127 mg. per cent, and the glucose tolerance test was normal. The blood urea nitrogen was 14 mg. per cent. The basal metabolic rate was normal. Urinary gonadotropin assay revealed the excretion of follicle-stimulating hormone to be 105 M.U. per 24 hours, which is castrate level. The urinary excretion of neutral 17-ketosteroids was subnormal, 2.5 mg. per 24 hours. Intravenous pyelography was normal. Papanicolaou vaginal and cervical mucus smears showed hypoestrogenic effect. The buccal mucosal smears disclosed a male distribution of nuclear chromatin. Cardiac examination was negative for coarctation of the aorta.

Under local anesthesia a culdoscopy was done with the patient in the lithotomy position, due to her resistance to the knee-chest position. Prior to the introduction of the

\*Presented at a meeting of the Brooklyn Gynecological Society, April 18, 1956.



culdoscope, the agglutinated labia were easily separated. The uterus and tubes were identified, but the ovaries could not be visualized. On removal of the culdoscope, a loop of intestine was noted coming through the opening in the cul-de-sac. Laparotomy was decided upon to rule out intestinal injury or perforation. At operation the uterus was noted to have maintained a fetal cervical fundal ratio (Fig. 1). There was a notch in the fundus of the uterus. The tubes appeared normal and free of convolutions. Rudimentary ovarian anlagen were found on the posterior surface of each broad ligament parallel to the tubes. They consisted of narrow (approximately 4 mm.) glistening, white fibrous streaks. The bowel was intact and free of damage. The cul-de-sac was repaired and the patient had an uneventful postoperative course. On discharge from the hospital she was placed on cyclic stilbestrol therapy.

After 3 months of estrogen therapy the patient has had monthly bleeding episodes, growth of pubic hair, breast development, and an increase of  $\frac{3}{4}$  of an inch in height. Her morale and psyche have been remarkably improved.

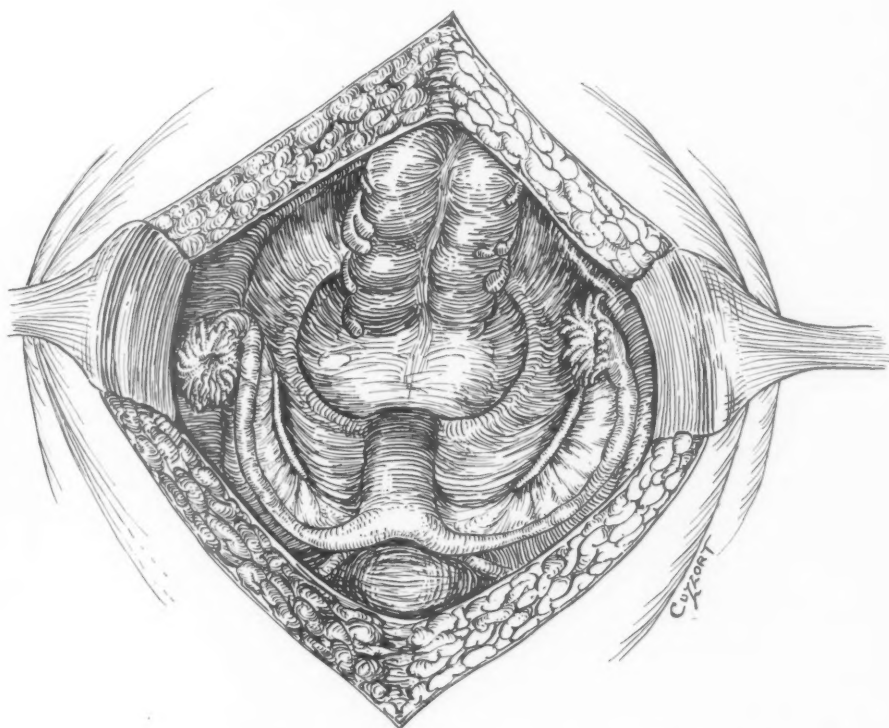


Fig. 1.—Drawing of internal genital organs as observed at operation.

### Comment

Sexual infantilism and short stature are features of other entities that are of hypothalamic, anterior pituitary, or gonadal origin. Consequently Fröhlich's syndrome, Laurence-Moon-Biedl syndrome, Simmonds' disease, infectious diseases involving the gonads in the prepubertal state, and eunuchoidism all must be differentiated from agenesis of the gonads. Panhypopituitarism can present a similar picture, which can be differentiated by the patient's delicate stature and absence of follicle-stimulating hormone.

The object of therapy is to supply the missing estrogen. Estrogen substitution therapy has been shown to be convenient, inexpensive, and easily regulated. In the case reported, the following schedule was employed:

First week	1 mg. daily
Second week	2 mg. daily
Third week	3 mg. daily
Fourth week	No therapy

Bleeding usually starts 48 to 72 hours following the withdrawal of stilbestrol. Wilkins<sup>6</sup> emphasized the importance of cyclic therapy to permit periodic endometrial breakdown and bleeding. Breast development, nipple pigmentation, and pubic hair can be expected. The external genitals, uterus, and tubes will mature. Stature is usually unchanged. With the development of the adult feminine figure and secondary sex characteristics, there is a decided psychological improvement and the likelihood of marriage is increased.

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## A TWENTY-YEAR FOLLOW-UP OF A PREPUBERTAL FEMALE CASTRATE

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A UNIQUE case was recorded in 1934<sup>1</sup> in which a girl of 9 had both ovaries removed in the space of a year. In each instance, torsion of a normal ovary was found.

Because of the scant information on therapy in the literature, the leading authorities in the United States were asked to give an opinion. In the light of present knowledge and the condition of the patient, a review of experienced opinions in the early thirties revealed some very interesting comparative ideas. It is also interesting, because the prevailing opinions in textbooks at the time were rather gloomy and pessimistic.

For example, Crossen's<sup>2</sup> textbook stated, "When the ovaries of newly born guinea pigs were removed, the breasts and the uterus and even the external genitalia failed to develop. Similar experiments on dogs and rabbits were the same; that is, prevented proper development of the uterus and the breasts. Complete absence of endocrine ovarian secretion results in the young in arrest of further development of sexual apparatus (infantile genitals). Menstruation fails to appear, female secondary sex characteristics develop incompletely; both in physical and mental characteristics a certain degree of masculinity may become noticeable." Graves<sup>3</sup> in his textbook stated, "Early castration prevents normal development of the genital system. It also produces changes in some of the other ductless glands, the most notable being that of the hypophysis in which there takes place an increase in the size of the anterior lobe. It is generally, though not universally, conceded that this hypertrophy of the hypophysis is the cause of the skeletal deviations and accumulation of fat that characterize the development of the eunuchoid type. Information regarding results of the castration before puberty in women is exceedingly meager." He concluded that castration before puberty would result in lack of development of the secondary sexual characteristics, including the breasts, and that the skeletal changes resemble those of the male castrate.

Emil Novak,<sup>4</sup> in response to a letter, replied in part, "I feel quite sure that I can give a reassuring prognosis in so far as the future life of this little patient is concerned. I do not think that the castration effects will be at all comparable to those which might be expected in the case of a male child. In spite of the fact that menstruation had not yet appeared, I think it reasonably certain that her female sex characters have been pretty well stamped. I do not think that the father need be worried about the possibility of any development of masculinization changes, although, from a theoretical standpoint, one would expect very little development of such secondary sex characteristics as mammary growth. It would seem foolish to try to predict exactly how the case is going to unfold. For the present, it would seem to me that no particular therapy would be indicated, although it is possible that later it may be advisable to resort to some form of organotherapy, such as the use of Theelin."

August A. Werner<sup>5</sup> replied in part, "Just knowing that her ovaries were removed, without knowing her present development and psyche, I rather hesitate to say very much. I believe that with proper treatment at the right time that we could carry her along nicely."

George V. Smith<sup>6</sup> replied, "I have talked the matter over with Dr. Frank A. Pemberton and others, and if the girl has nothing done for her, we think the chances are that she will fail to develop secondary sex characteristics, chiefly pubic and axillary hair and female contour. We assume that she would be rather obese and that she may develop

minor endocrine disturbances related to the hypophysis. It is more than likely that she would be, if anything, mentally above average, judging from the recorded mentality of eunuchs. It is also more than likely that she will be physically larger. As to the possibility of obesity, I do not think we can say definitely what will happen. My guess would be that she would have no neurological disturbance. As to the possibility of treatment, two things present themselves: first, the administration of the ovarian hormone, and, secondly, the transplantation of ovarian tissue. Now that we have potent sex hormone in the form of Amniotin, Theelin, Progynon, and Theelol, it ought not to be difficult to control that angle, except from the point of view of expense. However, if she receives sufficient estrin, it is not unlikely that she will have uterine bleeding, although that is entirely conjectural. On the whole, I should be inclined to give her estrin by mouth in the form of Amniotin in oil, Progynon, or Theelol, in amounts up to 500 units a week for the next two years, gradually increasing the dose to 1,000 units a week by the time she is 13. Concerning the possibility of ovarian transplantation, it might be better to wait until the approximate age of puberty, relying solely on estrin by mouth."

Robert T. Frank<sup>7</sup> replied, "As you say, these cases are extremely rare. The only cases which bear some analogy to this are three children, on two of whom I had to remove ovarian malignancies, and the third had an inoperable case of myxosarcoma of the mesentery. In all three, complete doses of x-ray for castration were given for the malignancies. Since this therapy in a child with mesenteric malignancy, five years have elapsed. In the other two, four and one-half years have elapsed. All three have shown normal growth, carefully controlled by anthropometric measurements performed every six months. All three are showing pubic hair. In two of them, the breast development appears approximately normal for such early adolescence. None of them has as yet menstruated. None of them, however, has shown any eunuchoid changes in her growth. Naturally, the next few years will be along eunuchoid lines or normal ones. As far as medication is concerned, there is nothing at present at our disposal which we would be warranted in giving to such children, since the female sex hormone would produce slight congestion in the genital region and would have to be continued indefinitely. Any preputiary medication would be out of the question, as this only acts in the genital sphere through the ovaries."

John C. Burch<sup>8</sup> stated, "In regard to the questions which arise as a result of the disturbance in balance brought about by the removal of the ovaries, it is my opinion that there will be a considerable disturbance in growth, hair development, and voice. In regard to the treatment, it seems to me that this case offers an unusual opportunity. At the present time, there is considerable doubt as to the existence of more than two ovarian hormones. The corpus luteum hormone, or progesterone, would have no effect on the growth changes, but estrin should have a marked effect on the growth changes. Recently, a report has appeared in the German literature by Dr. Kaufmann, in which he has been able to produce all the phenomena of menstruation in castrated women by injections of estrin and progesterone. He obtained these results by injecting 10,000 units of estrin in 1 c.c. of oil twice a week. It is, of course, unreasonable to think that injections of Theelin, which contains only 50 units to the c.c., would do any good when Kauffmann has clearly shown that the amount necessary would have to run about 20,000 units a week. It seems to me that it would be wise to give about 400,000 units a week for the next year and then start gradually increasing until she is receiving the full 20,000 units a week when she is 15 years of age."

Frederick L. Hisaw<sup>9</sup> wrote, "Information on this type of case is so meager that I hesitate to hazard a guess as to what may develop. I feel quite sure that it will not be possible to correct the condition of castration to the point of restoring normalcy. Especially is this true of the secondary sexual characteristics. I do not believe that she will be at as great a social disadvantage as our boys who come to this misfortune. Her voice will remain normal and the contour of her body, although it may not be as well proportioned as normal, yet will be more feminine than masculine. I rather expect that the results will be in her favor in this respect. As to any other suggestions, I am quite sure that it would be only a guess on my part to predict."



E. B. Woods<sup>10</sup> wrote, "The recent literature has shown that in castrated animals there is an involution of the anterior lobe of the pituitary. As I recall, this work has been studied by Van Dyke, of the University of Chicago. Because of the three-point relation of thyroid, pituitary, and ovary, it would seem advisable to administer ovarian extract until well past puberty, and probably until attainment of full growth is evidenced. As you know, castrated animals have a tendency to the asexual type. The female resembles the male, and vice versa. Furthermore, we know that prepubertal castration has a tendency to dull the mental facilities and destroy the initiative. So far as structural growth is concerned, I believe the literature shows nothing to indicate that this will not be normal, except of course for the tendency toward obesity."

Leo Loeb,<sup>11</sup> of Washington University, wrote, "When the age at which normally puberty occurs has arrived, the intermittent and cautious use of Theelin may be considered. Until then, it might be best to follow the metabolism of the patient and to administer small doses of thyroid substance, if a decrease in metabolism should be noticed."

H. M. Evans,<sup>12</sup> of the University of California, wrote, "I feel unable to suggest anything for your patient. The very distressing menopause symptoms which come on at the expected time, or acutely after surgical ablation of the ovaries in adult women, have of course, as you know, been relieved by hypodermic administration of folliculin, but one would not view with equanimity the prospect of a continuous therapy of this sort."

R. J. Crossen<sup>13</sup> of St Louis wrote, "I have had two cases of the type you mention. Both were placed on whole ovary Emplets, 5 grains, Parke, Davis & Company, twice daily, with excellent results. A basal should be taken every six months and thyroid supplied if needed. If symptoms develop, more active treatment is needed, consisting of Theelin and Lipo-Lutin hypodermically."

Edgar Allen,<sup>14</sup> of Yale University, wrote, "Although it would be very interesting, indeed, to try the effect of Theelin injections on this girl, I cannot convince myself at the present time that it would be the best thing from her point of view. If she were my own daughter, I would not do so unless some definitely disturbing symptoms develop. There is little reason to believe that there should be any such development if she properly understands the situation."

Excerpts from a letter written by the patient in 1954 contained the following pertinent information:

"I was born on Oct. 4, 1923. My height is 5 feet, 3 inches, and my weight varies between 106 and 109 pounds. My skin does not appear to be thin. When I was around 12 or 14 years old, I took medicine suggested by a child specialist. This medicine, no doubt, had hormones in it. It was to be taken daily. Unfortunately, I did not take it consistently, nor over a period of more than sixteen months. In January, 1952, when I first saw Dr. V., he prescribed an estrogen pill. This I have taken since that time. It is taken the first twenty days of every month. This enabled me to have my first menstrual period, which is normal. This usually lasts for about four to five days. Since taking this medicine, there has been a marked development of my breasts. Dr. V. remarked they were about average in size. Prior to the medicine, they were underdeveloped. In relation to the pubic hair, I would say it is slightly below average in amount. The axillary hair is normal. I was married on Aug. 21, 1953. There was a slight adjustment period in our sexual adjustment. However, I feel this has been normal and is satisfactory for both of us at this time."

A communication from Dr. V. in 1955 gives a good picture of the patient at the end of a twenty-year period after the castration.

"This first record I have in my own file, in regard to Mrs. V., is as follows: I saw her on Sept. 5, 1950, at which time she was 26 years of age. She had obtained her Masters Degree at V. University and was doing social work in Ohio. In 1950, she said she had no nervousness but had been rather nervous at school during the last year. She said she had received no medicine since the age of 9 years, yet on further questioning I found



out that Dr. H. gave her some gelatin capsules for two years when she was 10 to 12 years of age. However, I do not know what this was. She had never menstruated; she had occasional headaches; she had a small amount of breast tissue but no great development. She did not want a pelvic examination at that time. She looked perfectly well and felt fine. I saw her again on Jan. 9, 1952, at which time she was 28 years of age and was still doing social work. At this time, she said she had normal vaginal secretion. She was at that time put on Estinyl, 0.05 mg., the first to the twentieth day of the month for every month then on (this was advised when I questioned one of the endocrinologists who was giving us our postgraduate work at Massachusetts General Hospital in 1951). I also at that time told her to keep a record of any flow, any breast changes, or vaginal secretion. The reasons for giving Estinyl were: (1) It would keep her breasts and bones more normal. (2) Vaginal secretions would improve, which would be helpful for her approaching marriage. It would make her more virile, but she had felt real good before we began these treatments. You might note at this time that she had sustained a spiral fracture of the right humerus, which healed normally, with complete union, on Feb. 2, 1952. After she took her tablets for twenty days, she stopped them and two days later she flowed for four days. Ten days from the starting of her menstrual period, she started the tablets again and took them for another twenty days, and a flow appeared. At the very outset, she thought that the breasts enlarged a bit after taking the medication, and also she felt more nervous, especially at what she called her period time. She said her nervousness seemed to take on a fluctuation of feeling now and was more like a cycle of feeling, a plateau or flattening of feeling. The breasts were definitely fuller. Her weight had stayed constant, however, and she felt fine and was interested in her work. In August, 1953, she was married. She flowed the first month of her married life. Her flow was a little heavier and with some variation, using two to three pads a day. She never had cramps (this would be expected, because we are assuming that she is not ovulating since there are no ovaries). There has been a slight increase in the axillary hair, but more increase in the pubic area. She says that there is some breast pain about the time of the flow. This never did occur before she took the Estinyl. She thought the skin on her face broke out a little more. On examination, the breasts were excellently developed and on vaginal examination the cervix is normal. The vaginal canal appears normal and is moist. The fundus of the uterus is not well palpated, but what can be felt of it seems to be normal."

This unique case is presented after a twenty-year follow-up. The castration occurred at a date when our knowledge was young and groping, as shown by the letters mentioned at the beginning of this report. The results in the last two letters give us a heartening answer and definite evidences that optimism can be expected in a situation such as this.

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209 WEST 34TH STREET.

## FRUCTOLYSIS OF HUMAN SPERMATOZOA IN SEMEN

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**T**HERE is an acute need for the development of truly scientific criteria of male fertility through improvement in the standards of sperm evaluation. Even clinical studies on infertility have shown that the assessment of the physiological aspects of semen is of prime diagnostic value. But it is only recently that a trend toward investigation of the physiological and biochemical aspects of semen has developed.

There is little information on the metabolic phenomena which form the secret of the life of the sperm. In bulls, it has been shown by Mann<sup>4</sup> that fructose disappears from semen incubated in vitro, and the rate of fructolysis as assessed by the colorimetric assay of the disappearing fructose forms a simple and convenient measure of the metabolic activity of spermatozoa. This report on fructolysis in the semen of bulls, as well as the preliminary studies with human semen by Birnberg and associates,<sup>1</sup> and also the work of Davis and McCune<sup>2</sup> on fructolysis of human spermatozoa, has prompted this investigation of the metabolism of fructose in human semen.

### Methods and Procedure

One hundred and twenty-five cases have been studied and are presented here to assess the rate of fructolysis in human semen, in relation to the number of sperm cells and their motility, for the purpose of showing that fructolysis of human semen may be used as a basis for the evaluation of sperm quality.

Husbands whose wives had not yet produced a child or else had failed to give birth to a second child were selected for the examination from the gynaecological out-patient department. Those who had signs of venereal disease were excluded from the investigation. These men were subjected to examination after at least three days of abstinence from intercourse. The age of the subjects varied from 20 to 50 years.

Fresh semen specimens were obtained in the department and collected in clean, dry, wide-mouthed bottles equipped with tight stoppers. The specimens were ejaculated directly into the receptacles by masturbation. The volume, cell concentration, motility and morphology were determined as soon as the specimens had liquefied.<sup>3</sup>

In every case the chemical analysis of the specimen was begun as nearly as possible to 30 minutes after ejaculation. The initial fructose content and the rate of fructolysis of spermatozoa were studied by the method of Mann.<sup>4</sup> This consists of incubating semen-buffer mixture at 37° C. and determining the fructose content hourly for three hours. The rate of fructolysis is assessed by the colorimetric assay of disappearing fructose, which forms a simple and convenient measure of the metabolic activity of spermatozoa.

## Results and Comment

Twenty-five of the 125 subjects were found to be azoospermic. The initial fructose values for these 25 cases were unusually high (Table I).

TABLE I. INITIAL FRUCTOSE CONTENT (MG. PER CENT)

SPERM COUNT, MILLIONS PER C.C.	NO. OF EXPERIMENTS	MEAN	RANGE
1-250	100	251.4	69.4-638.4
0	25	552.8	312.5-682.3

The normal rate of fructolysis in human semen varied from 1.1 to 1.9 mg. of fructose utilized per  $10^9$  sperm cells in 1 hour at  $37^{\circ}$  C. The fructose utilization in semen was directly related to the sperm concentration and the motility of the sperm. A reduced rate of fructolysis was seen in semen of poor quality (Tables II and III).

TABLE II. THE RELATIONSHIP OF SPERM CONCENTRATION TO FRUCTOSE UTILIZATION

SPERM COUNT, MILLIONS PER C.C.	NO. OF EXPERIMENTS	FRUCTOSE UTILIZATION PER HOUR PER C.C. (MG.)	
		MEAN	RANGE
Less than 20	28	0.0056	0.0011-0.0129
20-59	16	0.0284	0.01-0.05
60 or above	56	0.1892	0.0676-0.4590

TABLE III. THE RELATIONSHIP OF MOTILITY TO FRUCTOSE UTILIZATION

DEGREE OF MOTILITY	NO. OF EXPERIMENTS	FRUCTOSE UTILIZATION PER HOUR PER $10^9$ SPERM (MG.)	
		MEAN	RANGE
High, 75-85% (+++ to ++++)	34	1.7	1.4-1.9
Intermediate, 45-70% (++ to +++)	36	1.4	0.9-1.7
Low, 10-40% (+ to ++)	40	0.62	0.32-0.91

Azoospermic semen did not utilize fructose and, as noted above, the fructose content of azoospermic specimens was rather high, the average of the 25 cases being 552.8 per cent (milligrams). The normal production of fructose by the seminal vesicles would indicate, according to the "fructose test" of Mann and Parsons,<sup>5</sup> normal stimulation by the testicular hormones. If these hormones are associated with spermatogenesis, the high fructose levels in the semen of these patients would suggest an obstructive aspermia, rather than aspermia due to testicular pathology. More extensive investigation may, therefore, lead to a simple "fructose test" which would differentiate between obstructive aspermia and aspermia due to agenesis or atrophy.

The interpretation of the results of sperm metabolism studies is complicated by the presence of several variable factors among individual semen specimens. The most important of these are the age of the sample at the time of analysis, the concentration of spermatozoa, and the motility of the sperm. Variations due to difference in age are eliminated by starting the experiment as nearly as possible to 30 minutes after the specimens were collected. The cell concentration factor can be eliminated by expressing the fructose utilization in terms of milligrams of fructose per  $10^9$  cells.

Semen is a unique experimental subject in that it is an animal tissue composed of only one type of cell, the spermatozoon, so that all metabolic measurements can be related specifically to sperm cells and the metabolic activities can be expressed in terms of cell numbers. Semen can be regarded as a uniform cell suspension with strictly defined cell density. Furthermore, spermatozoa are endowed by nature with the highly specialized biological functions of fertility and motility, which not only distinguish them sharply from other cells, but at the same time set at the disposal of the investigator two clearly defined and specific biological criteria of sperm activity to be used in conjunction with his observations of metabolic activity.

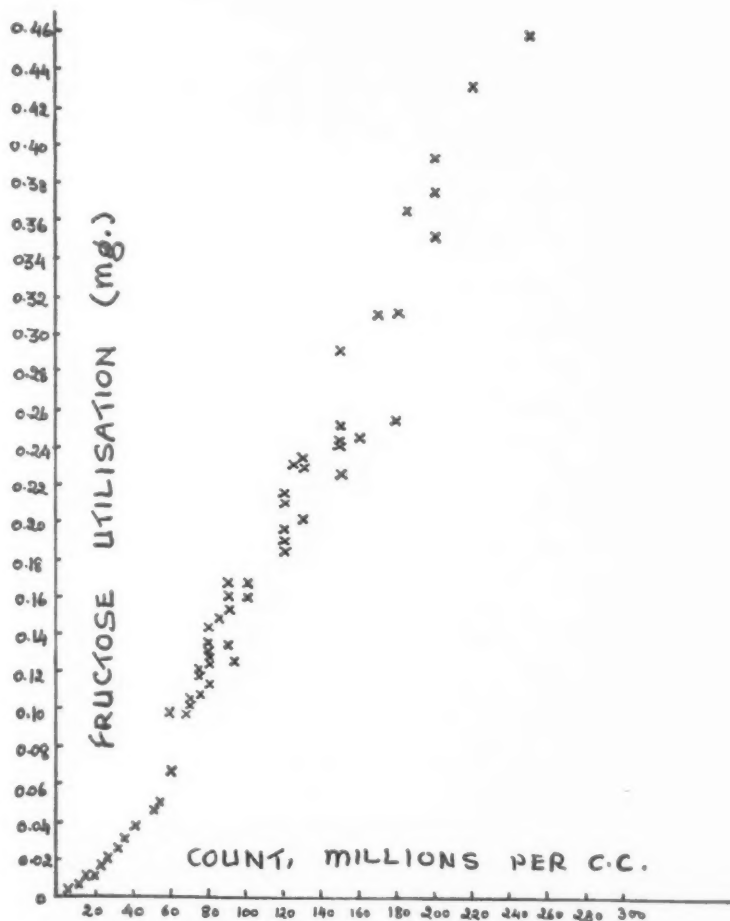


Fig. 1.—The relationship of cell concentration to fructose utilization.

The normal rate of fructolysis in the present studies has been found to be 1.1 to 1.9 mg. of fructose utilized per  $10^9$  sperm cells in 1 hour at  $37^{\circ}$  C. This compares quite closely with the figures (1.4 to 2.0 mg. per hour per  $10^9$  spermatozoa at  $37^{\circ}$  C.) obtained for bull semen by Mann<sup>4</sup> under the same conditions.

The fructose utilization per hour per cubic centimeter of semen with counts of less than 20 million per cubic centimeter is significantly lower (0.0011 to 0.0129) than the normal values (Table II). Fig. 1 also brings out clearly the strong positive association between the cell concentration and the total fructose utilization.

In addition, the fructolysis index (milligrams of fructose utilized at 37° C. in 1 hour by 10<sup>9</sup> sperm cells) is associated positively with the motility of the sperm, as shown in Fig. 2. The rate of fructolysis in semen showing a high degree of motility is almost three times that of specimens which have low motility (Table III).

The multiple regression equation for fructose utilization ( $x_1$ ) on count ( $x_2$ ) and motility ( $x_3$ ) is:

$$x_1 = -0.02287 + 0.001848 x_2 - 0.000055 x_3$$

The squares of the two partial correlation coefficients are:

$$r^2_{12.3} = 0.9429$$

$$r^2_{13.2} = 0.002$$

This means that, if motility is kept constant, variations in count account for 94 per cent of the variation in fructose utilization, whereas, if the count is kept constant, variations in motility account for only 0.2 per cent of the variation in fructose utilization.

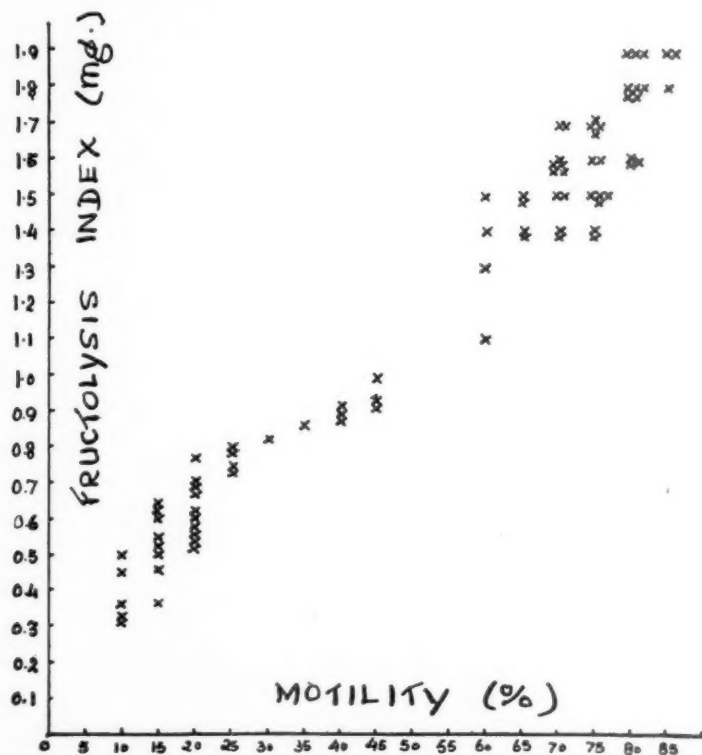


Fig. 2.—The relationship of motility to fructose utilization.

From the analysis of this series it appears that the cell count and the fructose utilization test are essentially equivalent investigations. Of the two, however, it is felt that the fructolysis determination, by directly indicating the functional behavior of the sperm cells, presents itself as a more promising tool in our attempts at a rational study of sterility. Despite the fact that the estimation of fructolysis is a somewhat complex procedure, it is a precise method to



evaluate the composite picture of a given sample. The fructolysis index obtained by relating the utilization to the cell number indicates the average metabolic activity of the sperm cells and even potentially the fertility of the individual.

### Summary

The rate of fructolysis in man affords a measure by which to evaluate the quality of the semen, as it has been found to correlate closely with cell count and the motility of the sperm.

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## HYSTEROSALPINGOGRAPHY WITH ETHIODOL

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THE position of hysterosalpingography in gynecological diagnosis has changed radically during the past 10 years. Most workers, including myself, have come to regard it as an integral part of any sterility investigation, because roentgenograms will give some information on the anatomical structure of the uterus and Fallopian tubes, whereas tubal insufflation merely shows their patency or occlusion.

Many gynecologists have begun to take uterosalpingograms in their offices or have been instrumental in having the contrast medium injected at the roentgenologist's office; they, therefore, have had to familiarize themselves with the advantages and properties of different opaque media.

### Search for an Ideal Medium

The search for an ideal contrast medium for hysterosalpingography has been going on for 40 years. One substance which has held the prime position in the field is Lipiodol, a 40 per cent iodized oil, which still is used extensively here and abroad. It has exhibited several disadvantages, however, which have caused investigators to search continuously for a different medium. The fact that it sometimes took many months, even years, before Lipiodol was absorbed from the peritoneal cavity is well known, and this occasionally led to the formation of foreign-body granulomas. Pulmonary oil embolism has also been reported.<sup>1, 2, 3</sup> Thus it is not surprising that investigators have been looking for a medium which would be free from such inherent dangers.

Erbslöh<sup>4</sup> experimented with different oils and sols and, after comparing their various characteristics, laid down the requirements for the ideal opaque substance in hysterosalpingography. He postulated that a medium should be nonirritating; it should be of low viscosity, so that it could be injected with a minimum of pressure; it should not show too much contrast, lest it "cover up" pathological structures on the posterior wall of the uterus; and, finally, it should have a low surface tension.

Some of these requirements were fulfilled by the water-soluble media which were introduced by Rubin<sup>5</sup> in 1941. Their advantage was said to be that, if inadvertently injected into the blood stream, they would cause no serious consequences, but they were unsatisfactory in other respects: for one thing, their contact with the peritoneum caused marked cramplike pains—an effect hardly ever observed with any oily medium.

I have used water-soluble media in a limited number of patients but have given them up for general use since the patients complained of very severe pain when the medium came in contact with the peritoneum; in one case the pain was so severe that the patient went into shock.

This pain appears to be due to the water-soluble vehicle and is comparable to that experienced by a woman upon spillage of blood from the fimbriated end of the tube (e.g., in ectopic pregnancy or retrograde menstruation.)

The admixture of a local anesthetic, as first proposed by Kjellberg<sup>6</sup> and recently taken up again by Erbslöh,<sup>7</sup> cannot be recommended, since any pain experienced by the patient may often serve as a warning signal to stop the injection.

The formation of foreign-body granulomas after the use of Lipiodol has been described several times, but the literature of recent years<sup>8-11</sup> has shown that foreign-body granulomas can also arise after the use of water-soluble media. Bergman and associates<sup>12</sup> reported on 18 patients who had undergone hysterosalpingography with a water-soluble medium. In these, foreign-body granulomas were histologically demonstrable in 16 of the 18 women; upon operation the lesions were seen in the uterus in 8 cases, in the tubes in 2, and in the ovaries in 7. These references may suffice to show that foreign-body granulomas are not caused by any particular contrast medium but may, on occasion, be observed after hysterosalpingography with any of the known contrast substances.

Water-soluble media are absorbed within 15 to 30 minutes after injection, a decided disadvantage in sterility studies, because this precludes the 24 hour film, the importance of which has been stressed by gynecologists and radiologists alike.<sup>13-16</sup>

### Introduction of a New Medium

Another product, Ethiodol,\* was introduced in Europe as early as 1939 under the name "Lipiodol ultra-fluide" or "Lipiodol-F." It did not become commercially available in this country until 1954, when it was first introduced during the annual meeting of the American Society for the Study of Sterility in San Francisco, California. Since that time, I have used it in 161 hysterosalpingographies. The results of this experience are reported in this paper.

Each cubic centimeter of Ethiodol contains 0.475 Gm. iodine. Its specific gravity at 15° C. is 1.280 and at body temperature (37° C.) it has a viscosity of 30.2 centipoises. Its fluidity is similar to that of distilled water. It is a straw- to amber-colored oily fluid which has the blandness and freedom from irritating qualities necessary in a contrast medium suitable for salpingography.

In absorption characteristics, it lies between Lipiodol and the aqueous media, usually disappearing from the peritoneum within from 45 to 60 days, depending on the amount used and on other factors. Its contrast value is excellent.

### Technique of Administration

In hysterosalpingographies with Ethiodol, I have employed the standard technique as advocated by Robins and Shapira.<sup>14</sup> A delayed film after 12 or 24 hours was taken, following their recommended procedure. In a few cases, where the 24 hour film was inconclusive, another one was taken 3 to 4 days later.

\*Ethyl ester of the iodinated fatty acid of poppy-seed oil. Data supplied by the manufacturer, E. Fougere & Co., Inc., 75 Varick St., New York 13, N. Y.

### Indications, Contraindications, and Precautionary Measures

As with all drugs introduced into the body for diagnostic or therapeutic purposes, certain precautionary measures should be observed to avoid serious mishaps. Since Ethiodol is an iodine compound, allergic reactions to this element may occur. I have never observed them, and they must be much rarer than in excretory urography. Dalsace and Garcia-Caldéron<sup>17</sup> suggested that allergic manifestations are more prone to occur with water-soluble than with oily substances because of their more rapid absorption. They also felt that one should refrain from using an iodine compound in patients with renal insufficiency, since the delayed elimination may lead to iodism.

Because the absorption of iodine from Ethiodol is minimal if it is employed in the proper dosage, hyperthyroidism and inactive tuberculosis need not constitute contraindications to its use; Dalsace<sup>18</sup> has even used hysterosalpingography in the diagnosis of latent genital tuberculosis.

In one condition, however, the use of any oily medium is contraindicated, namely, in patients who give a history of intermenstrual bleeding. The possibility of injecting oil into an open venous sinus is always present, and in such cases pulmonary oil embolism may occur; it has never been reported with Ethiodol. I therefore have desisted from performing hysterosalpingography with an oily medium on women who have given a history of (1) a recent miscarriage (less than 6 weeks), (2) a recent curettage (less than 6 weeks), and (3) intermenstrual bleeding (spotting at ovulation time is disregarded). In these patients I have used other methods to establish a diagnosis.

Some investigators have recommended hysterosalpingography to diagnose intra- or extrauterine pregnancy. I do not believe that it should be employed under such circumstances since the diagnosis can be made by means less likely to inflict harm upon the patient. For the same reason, hysterosalpingography is contraindicated where an endometrial carcinoma is suspected, since the danger of retrograde dissemination of cancer cells is ever present.

If the patient has gone through a recent episode of salpingitis, the infected exudate may be ejected into the abdomen. It therefore is imperative that a careful history be taken and that a leukocyte count and sedimentation rate determination be done to prevent such an occurrence. Those of my patients who exhibited a purulent discharge, pain, and an increased sedimentation rate were first treated with antibiotics and vaginal short-wave applications until the acute symptoms subsided and remained quiescent through two menstrual periods.

Another factor which should be investigated before the use of hysterosalpingography is the possibility of an infestation of the vagina with *Trichomonas vaginalis* or *Candida albicans*. These microorganisms are generally confined to the vagina, and any intrauterine manipulation may introduce them into the uterine cavity.

### Findings

In more than 161 hysterosalpingographies, Ethiodol has proved to be a very satisfactory opaque medium for general use in gynecological diagnosis.

I have done the vast majority (129) of these hysterosalpingographies as part of sterility investigations (Fig. 1); the remaining 32 were done for general gynecologic diagnosis (Fig. 2). The conditions encountered are shown in Table I.

Roentgenograms obtained after the use of Ethiodol showed far more contrast than those taken after injection of a water-soluble medium. Whereas

TABLE I. ANALYSIS OF 161 HYSTEOSALPINGOGRAPHS WITH ETHIODOL

CONDITIONS ENCOUNTERED*	NUMBER OF CASES
No pathological findings	81
Bilateral tubal occlusion:	
At cornual end	18
At fimbriated end	14
Unilateral tubal occlusion:	
At cornual end	6
At fimbriated end	14
Stenosis of internal os or angulation of cervical canal	18
Hypoplastic uterus	2
Incompetent internal os	4
Endometrial hyperplasia	4
Tumors of uterus (polyps or myomas)	14
Malformations	7
Lithopedion	1

\*Some patients had more than one condition.

Ethiodol, when "spilled" from the Fallopian tube, appears as well-circumscribed droplets, the water-soluble media present an image like a broad, undulant band of low contrast. Erbslöh<sup>7</sup> and Finkbeiner<sup>19</sup> have stated, and I agree, that it is necessary to learn a completely new method of shadow interpretation when reading films made with water-soluble media. Fluoroscopy, when Ethiodol is used, is not absolutely necessary, but the quick absorption of the water-soluble media makes fluoroscopy (and thus a prolonged roentgen exposure) imperative.



Fig. 1.



Fig. 2.

Fig. 1.—Hysterosalpingogram with Ethiodol. Normal uterine cavity, both tubes patent.

Fig. 2.—Uterine cavity showing filling defects due to a submucous myoma and coexisting endometrial hyperplasia.

In the diagnosis of uterine and tubal pathology, Ethiodol hysterosalpingography was superior to the air-insufflation test and to salpingography with water-soluble media.

Among all these patients (who, I admit, were properly selected), I have not seen any intravasation of the contrast medium or any exacerbation of a chronic salpingitis.



Ethiodol is absorbed much more quickly from the peritoneal cavity than are other oily contrast media. Palmer<sup>20</sup> found its average stay to be about three menstrual cycles; in exceptional cases it might go beyond 100 days. I have found that the time of complete absorption depends upon the amount of substance injected. In the great majority of cases, I have used only about 6 c.c. of Ethiodol, of which 2 c.c. remained in the cannula. Thus, only 4 c.c. of contrast medium was necessary to obtain clear films. My own experience has shown that, in the majority of patients, the oil had disappeared after about 60 days, and that no trace of it could be detected on subsequent roentgenograms.

### Summary and Conclusions

From this study it appears that Ethiodol as a contrast medium in hysterosalpingography has superior contrast value, making interpretation of films simpler and permitting the taking of 24 hour films. I have found it superior to the Rubin test in the diagnosis of pathological conditions and have observed no notable degree of pain, or intravasation, or exacerbation of chronic salpingitis with its use. The material was absorbed from the peritoneal cavity in about 60 days.

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## LEIOMYOSARCOMA OF THE UTERUS\*

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THE problem of leiomyosarcoma of the uterus is of immediate importance. Although rare, it is the subject of daily discussion. The threat of sarcomatous change in a benign myoma is the most frequent reason given by the over-enthusiastic surgeon for urging hysterectomy for an otherwise innocuous myoma.

This attitude is based on a false interpretation of the frequency with which benign myomas undergo a lethal sarcomatous change. This is not a mere academic question of the classification of uterine tumors. Upon the determination of the true probability with which lethal sarcomatous change occurs in myomas will rest the decision as to whether hundreds, perhaps thousands, of women are being operated upon unnecessarily.

This false interpretation is due, in part, to confusion in the reporting of sarcomas of the uterus.

1. At least 7 neoplasms of the uterus, although they have nothing to do with leiomyosarcoma, are indiscriminately grouped under the heading of "sarcoma of the uterus." The total thus obtained is used in estimating the incidence of sarcomatous change in a myoma.<sup>1</sup>

2. Many cases of true leiomyosarcoma arise in uterine tissues in which there is no myoma present. They are also included in the statistical calculation.

3. Last, and most important, the diagnosis of leiomyosarcoma has been based on varying degrees of cellular change in a myoma, changes which are not truly neoplastic in nature but are due to degenerative processes.<sup>2, 3</sup> It is this group to which we shall give our present attention.

The question to be decided is whether cellular atypicalities in a myoma justify the diagnosis of leiomyosarcoma or whether evidence of invasion is necessary for such a diagnosis. The standard by which the lethality of the tumor will be determined is the correlation between the characteristics of the tumor found on pathologic examination and the postoperative fate of the patient. This, for clinical purposes, is the best criterion. While certain potentially lethal tumors which showed only cellular atypicalities may have been caught at such an early stage that they were completely eradicated, others of these should have gone on to destroy the patient. This we have failed to find.

\*Presented at a meeting of the New York Obstetrical Society, Nov. 13, 1956.

TABLE I. SARCOMAS OF THE UTERUS AT THE PRESBYTERIAN, SLOANE, AND FRANCIS DELAFIELD HOSPITALS

Carcinosarcoma	11
Endometrial sarcoma	2
Stromatous endometriosis	3
Mixed mesodermal tumors	4
Malignant teratoma	1
Hemangiosarcoma	1
Reticulum-cell lymphosarcoma	3
Leiomyosarcoma	32
Total	57

TABLE II. SYMPTOMS OF LEIOMYOSARCOMA

SYMPTOMS	TYPE OF TUMOR																																
	MURAL														INTRA-LIGA-MENTOUS			CERVICAL			SUBMUCOUS PEDUNCULATED												
															15	16	17	18	19														
	CASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Distant																																	
Mass	X	X					X	X	X	X	X			X							X				X								
Pain		X	X	X			X	X	X	X	X										X				X								
Urinary	X							X						X																			
Bleeding	X		X			X						X									X		X	X		X	X	X	X	X	X	X	
Fever																					X												
Cachexia																					X												
None																																	

\*In this one case without symptoms on examination, pain and fever occurred before operation was performed.

In the literature in many reports this sharp division is not made. In the few in which this point is carefully studied, nearly all the patients whose tumors showed only cellular atypicalities have lived, whereas those whose tumors showed invasion have died of the disease.<sup>4</sup>

### Material

There have been observed in the Presbyterian Hospital and the Sloane Hospital between 1917 and 1955:

57 cases in which a diagnosis of "sarcoma of the uterus" was made (Table I).

32 of these were leiomyosarcoma.

23 of these originated in a myoma.

1 of these was doubtful (possibly secondary to a mesothelioma of the chest).

3 of the 22 showed only cytologic atypicalities. All of these patients are alive 2 to 20 years after operation.

19 specimens showed evidence of invasion. All of these patients except one (followed 2 years) are dead.

The fallacy of accepting cellular atypicalities as a criterion of sarcomatous change is further emphasized by these cases where a myoma in which there were no atypicalities whatsoever either recurred or metastasized. During this study 5 such cases were found and are the subject of a separate study. Other similar cases have been reported.<sup>5-9</sup>

The 9 patients in whom there was no evidence of a pre-existing myoma all had tumors which were grossly or histologically invasive and are all dead of the disease.

### Incidence

Among more than 15,000 clinically diagnosed cases of fibromyoma there occurred 19 cases in which there was a lethal sarcomatous change, an incidence of 0.13 per cent or 1:800.

If 5 cases of myoma with no histologic atypicalities but which had recurred or metastasized are included, the incidence would be 24:15,000 or 0.16 per cent.

The 15,000 cases which are used as the statistical base include only the cases which were recorded. The estimated number of myomas in patients admitted to the hospital from 1917 to 1955 is over 69,000. This is 20 per cent of 348,794 females over the age of 14.<sup>10</sup> Since the actual number of patients with myomas is unknown, we can only say that it is much greater than 15,000 and that therefore the incidence of leiomyosarcoma in myomas is much lower than 0.13 per cent.

Further evidence of the rarity of leiomyosarcoma of the uterus is furnished by the fact that this disease has never been discovered in this institution in 8,160 autopsies performed on women.

### Clinical Picture

The presence or absence of a pre-existing myoma did not affect the clinical picture. All 32 patients had symptoms (Table II). Pain, fever, and urinary disturbances were not distinguishable from those which occur in acute red degeneration of a myoma. Bleeding from the submucous sarcomas was no different from that which occurs with a benign tumor.

A preoperative diagnosis of sarcoma was mentioned in 3 cases but was the principal diagnosis in only one.

Diagnostic curettage was of little help. It was performed in 15 cases. In 3 cases the gross appearance of the curettings suggested carcinoma of the endometrium and led to an immediate hysterectomy.

In one case a frozen section established the diagnosis of round-cell sarcoma.

In 11 cases the curettage was negative. In 8 of these it did not affect the course of the treatment. In 3 cases operation was delayed 6 to 15 months by the negative findings.

At operation, signs of infiltration of parametrial tissue and abdominal extension and metastases were frequently observed. The cut section of the tumor showed varying degrees of necrosis. The principal characteristic sign was the presence of hemorrhage in the tumor, especially in the form of hemorrhagic streaks which traversed the cut section.

### Treatment

Treatment was of little importance. In the cases of "pseudosarcoma," "cellular myoma," any form of operation was curative—myomectomy, supra vaginal hysterectomy. In the cases of true sarcoma, the extent of the operation did not affect the result. All patients (but one) died of the sarcoma. There is no reported experience with radical hysterectomy.

Supplementary external x-ray therapy brought about no cures. It partly controlled an abdominal mass (7 years) and a pulmonary metastasis (5 years).

### Comment

From our observations we agree with those who require evidence of invasion to justify the diagnosis of sarcomatous change in a myoma.<sup>11</sup>

The tumors which showed only cytologic atypicalities have failed to recur after myomectomy, supravaginal hysterectomy, or complete hysterectomy.

Tumors in which there was evidence of invasion have all recurred and have caused the death of the patient. (In our cases one patient is still living 2 years after operation.)

While this standard is open to objection, it is the best one from the clinical standpoint, the health of the patient being our principal consideration.

### Conclusions

1. In a myoma of the uterus, the presence of cytologic atypicalities without evidence of invasion is not sufficient grounds for the diagnosis of sarcoma of the uterus.

2. The incidence of lethal leiomyosarcomatous change in a myoma in our series was less than 0.13 per cent or one in 800 cases.

3. With such a low probability of sarcomatous change in a myoma, hysterectomy for small innocuous myomas is not warranted.

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### Discussion

DR. HOWARD C. TAYLOR, JR.—There is one clinical situation arising with sarcoma of the uterus to which I think Dr. Corscaden did not refer. This concerns the patient who has a hysterectomy for supposedly benign myomas, the true nature of which is not recognized until later when she has a metastasis. In a series reviewed from the Roosevelt Hospital a number of years ago there were 2 or 3 such patients. In these the fibroid was regarded as benign even by the pathologic laboratory, which either cut sections from the wrong area or else misinterpreted the pathologic findings.

Perhaps Dr. Corscaden's attack on the "unnecessary hysterectomy" also deserves comment. He is perfectly right in condemning the argument that a benign fibroid should be removed because it might become malignant. The problem is rather whether what one is palpating is really a fibroid. If one makes an error, once in perhaps 200 cases, it may be argued that it would have been better to have operated on all 200, even if in 199 it was "unnecessary."

In the last year I have had the unhappy experience of finding that a patient whom I had been following for the last three or four years with multiple fibroids had developed an ovarian carcinoma. On account of my conviction that I am dealing with fibroids, there was undoubtedly a delay of some months in instituting surgical treatment. I can think of at least one other similar case in the practice of another gynecologist.

This is a little off the main subject, but I do think we must rather often recommend hysterectomies that may prove to be "unnecessary," not because we are afraid that malignancy may eventually develop, but rather because we are not absolutely certain of the diagnosis at the time.

DR. J. EDWARD HALL.—As usual, Dr. Corscaden has given us a classical presentation. I think we have all enjoyed it. I believe, however, as far as criteria are concerned, that possibly we are in the same category here as to some extent we are with intra-epithelial carcinoma in its relationship to invasive carcinoma. We should all be very much alerted to the fact that just because a patient lives does not necessarily mean that the tumor mass which was removed was a benign lesion. To some extent, this takes us into the field of philosophy concerning neoplastic disease, as to whether the neoplastic process is of the same degree and extent of malignancy from its onset or do the extent and degree of malignancy increase as time goes on?

For that reason I wonder whether possibly some of these tumors which are classified as cellular myomas, such as the one described in the case report this evening by Dr. Goldberger, might well be malignant and that the patient is alive because that tumor has been removed. Dr. Taylor has already mentioned a case where the patient did die although histologically the pathologist reported this tumor as benign.

I do not think we know the answer today as to just how to classify these tumors when we look at them through the microscope, whether the particular one is malignant or benign. It is very likely there are different gradations of malignancy histologically and many of these patients are alive today because the early tumor of low-grade malignancy was removed before the disease progressed.

I would also like to put in a word of caution about frozen section. It has been mentioned very clearly and consistently by Dr. Corscaden that it does not always give us the answer. I do not think that the clinician should be lulled into a false sense of security by frozen section reports on this type of tumor any more than he should on many of the ovarian tumors.

DR. CHARLES MCLANE.—I think that Dr. Corscaden has done a remarkable piece of work in gathering together these cases of leiomyosarcoma. I am amazed however that he does not divide his cases into two groups. It has seemed to me from what I have seen and what I have read that in the younger age group, patients who are still menstruating, where the sarcoma is an incidental finding to a myomectomy or a hysterectomy for myomas the patients all do very well. Many cases have been reported in which a simple myomectomy apparently cured the condition. However, in the postmenopausal group of much older women the occurrence of a sudden growth of the uterus and/or bleeding is usually fairly hopeless to treat no matter what is done. Unless the cases are divided into these two groups the results are very difficult to interpret or understand.

DR. EDWARD G. WATERS.—I would not feel too happy about the future of any patient with myosarcoma, despite a short-term cure. The poor long-term salvage has been impressed upon me by three experiences, one of which may be worth repeating here.

In 1932 I removed a very large fibromyomatous uterus, reported as a cellular fibromyoma. Eight years later, I reoperated for a large mass in the right upper abdomen, which exhaustive studies showed to be unrelated to the liver, gall bladder, intestinal or genitourinary tracts. The tumor was the size of a grapefruit and retroperitoneal, with attachment to the right kidney, requiring resection of its lower third. Pathologically, it was considered a slow-growing spindle-cell sarcoma.

A year later, a large mass appeared in the pelvis between the bladder and the sacrum. Removal was difficult, and much of the adherent bladder fundus was sacrificed. Despite this, the patient soon voided without difficulty and attained normal bladder capacity. The tumor again was a spindle-cell myofibrosarcoma showing many mitoses. She then remained free of symptoms for seven years. There now developed a slowly progressive enlargement of the right lower extremity, the mid-thigh measurement attaining more than 80 cm., although her usual weight of 260 pounds had dropped to 245 pounds.

Examination showed a huge lower extremity with congestive discoloration, phlegmonous thickening of the tissues, extremely dilated veins, and a large indolent ulcer covering most of the lower third of the leg. A large mass again filled the pelvis and right side of the lower abdomen, easily palpable despite the marked obesity. Except for the involvement of the lower extremity, the findings were much the same as 7 years earlier.

She refused operation for nearly 2 years, when the lesion seemed completely hopeless. At operation, the right internal iliac vein was involved and sacrificed. The operation was bloody and difficult, and further complicated by a second similar but smaller tumor located posterior to the transverse mesocolon. Removing this exposed the ureter and kidney, aorta and vena cava, and a near-fatal tear was made in the vena cava. Postoperative radiation was again employed. In 1952, there was another recurrence at the vaginal vault, and a second retroperitoneal tumor at the level of the third lumbar, below the pancreas. Its removal was not easy, and required dislocating the inferior mesenteric vessels to the right, and again dissecting the tumor from the aorta-vena cava. Two thousand cubic centimeters of blood was given during this abdominopelvic procedure. These tumors presented a picture of round-cell sarcoma with extension to the pelvic fascia, bladder, and pancreas. The lower extremity gradually returned to normal and the ulcer healed in a year.

In 1954, I saw her again with severe pain and symptoms indicating lumbosacral root disturbance, and referred her to the Neurological Hospital for care. Operation there revealed a recurrent sarcoma involving the lumbar spine. She recovered from the operation but has a residual "cord bladder" with no urinary control. She was returned to my reluctant care by her physician recently, and has recurrence in the third and fourth lumbar vertebrae, and a healing pathologic fracture of the right femoral neck. She is fairly free of pain and looks well. Her weight, now 220, varied from 230 to 260 pounds through these surgical episodes and made all operations more formidable.

To summarize, here is a patient with recurrent leiomyosarcoma, definitely dating back 16 years and very probably 24 years to the "cellular myoma" first removed. The recurrences have been labeled as round and spindle cell, depending upon the site studied, have been in

various retroperitoneal sites in the abdomen, and now involve the lumbar spine and the right femur. The patient remains reasonably well despite a cord bladder and pathologic but healing fracture and, until 2 years ago, was an important factor in a business in her hospital-free intervals. This record confirms Dr. Corscaden's belief that a hysterectomy should always be total if indicated at all, and that myomectomy should be reserved for benign tumors in young women during childbearing years.

This, with two other experiences, while serving as a warning against overoptimism, since lapses of 7 to 10 years may intervene between recurrences, also indicates to me the salvage value of repeat radical surgery for prolonging useful life.

DR. CORSCADEN (Closing).—This is simply a report of experience; an attempt to translate that experience into this matter of definition. There are no myomectomies in the series, so that all I can discuss in the way of myomectomy is by speculation and from the observations of others. I do think that if it is important for a young woman to have children and there is no evidence of invasion in such a tumor which has been removed by myomectomy, you are entitled to take the same chances as one is entitled to take with an intraepithelial cancer of the cervix.

One faces two important problems, the health of the mother and her capacity for future childbearing. I see no other reason for performing a myomectomy. The practical problem is to balance one evil against the other.

Concerning the age, the mean age was 49. The youngest was 33. These are not all tumors of old women, so that the problem is not restricted to the menopausal patient.

With regard to Dr. Taylor's mention of the ovary, I heartily agree that unless a mass in the pelvis is definitely uterine, it should be regarded with suspicion. In multiple lobulated fibroids one indication for operation is the possibility that one of the lobules may not be a fibroid but may be an ovarian tumor. But this problem tonight is a little different. What I am driving at is the case of the woman who comes to the physician with some nongynecologic condition. There is nothing the matter with her except a little shortness of breath, a cold in the head, etc. The careful medical man, in his general examination, finds the pelvic mass. He does not wish to advise treatment. He refers her to a gynecologist. What will the gynecologist tell that woman? That is the consultation I am talking about. One man will say, "You had better get it out because this is very likely to turn malignant and jeopardize your life." Another one will say, "The incidence of malignancy is so low that the operation which you will have will do you much more harm than the protection it would give."

Prophylactic hysterectomy may ultimately become a proper procedure as a protection against cancers of the cervix and endometrium, but an innocuous myoma furnishes no such excuse.

## LYMPHOSARCOMA OF THE UTERUS

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**L** EUKEMIC infiltration of subclinical degree involving the uterus is not particularly uncommon since practically all organs may show involvement of this type in terminal cases of lymphocytic neoplasia with blood stream involvement. However, lymphomatous involvement of the uterus with the production of signs and symptoms exclusively or primarily involving this organ is highly unusual and when encountered may pose difficult problems in diagnosis and therapy.

The subject was apparently not uncommon in the early German literature and the best report available is that of Walther<sup>1</sup> who in 1934 summarized existing literature concerning lymphosarcoma of the female genital tract. He was able to find 5 cases of lymphosarcoma of the uterus previously reported and added to these one case of his own. These were cases in which the uterus was primarily involved, with the production of symptoms similar to those encountered in carcinoma of the corpus. The lesions in these cases were nodular and circumscribed and he felt that they had actually originated in the uterus, probably from pre-existing lymphatic follicles in the endometrium with secondary involvement of adjacent structures and retroperitoneal lymph nodes.

References in the English literature are very few. McDonald and Waugh<sup>2</sup> reported a case in which the major symptom was uterine bleeding and the curettings disclosed stromal replacement of the endometrium by lymphocytes. Studies finally established the diagnosis of chronic lymphatic leukemia with infiltration of the endometrium. Epperson<sup>3</sup> reported a case in which prolonged vaginal bleeding was due to lymphomatous infiltration of the uterus. Walton<sup>4</sup> reported 2 cases in 1953, one an isolated uterine lesion, the other associated with leukemia. Aside from these, the literature is strangely silent about these lesions and the subject seems to have lapsed into obscurity. We are adding the following case to the available literature not only because of the rarity of the disorder but also because its recognition has practical importance.

### Case Report

The patient was a 35-year-old white housewife who was admitted to the Virginia Mason Hospital because of excessive vaginal bleeding. This had continued for a week and she became pale and felt dizzy. The past history included the treatment of a malignant tumor of the maxillary sinus by irradiation two years previously. Biopsy was said

to show a transitional-cell carcinoma. There had been no local recurrence and no evidence of node involvement. Examination disclosed the fact that the uterus was enlarged (two to three times) and somewhat asymmetrical. Other than this and evidence of severe anemia, physical examination and laboratory studies showed no abnormalities. Adequate blood replacement was given and a curettage carried out. Some of the pieces were large and polypoid and in these there was a curious replacement of the stroma with cells resembling lymphocytes. These were closely packed and slightly pleomorphic. This infiltrate had obliterated or partially effaced the normal architecture and glands were rarely seen. It was decided that the lesion probably represented lymphomatous infiltration of the stroma. Vaginal bleeding which had ceased after curettage recurred in a few days and was again profuse with clots. She was again treated with transfusions and a hysterectomy performed.



Fig. 1.—Lymphosarcoma arising in endometrium of uterus. Sharply circumscribed solitary lesion.

*Pathologic Findings.*—The uterus weighed 234 grams. A sharply circumscribed tumor 5 cm. in diameter was present in the fundus, which was pale tan in color, soft, and somewhat friable. It extended a moderate distance into the underlying myometrium (Fig. 1). Microscopic features of the tumor were similar to those noted in the fragments obtained by curettage. A diffuse infiltrate of slightly pleomorphic cells resembling lymphocytes with partial effacement of endometrial glands comprised the tumor mass (Fig. 2). There were extension and infiltration into the underlying myometrium but only for a short distance. Except for a zone of necrosis along the surface, the tumor was entirely viable. No other nodules were encountered aside from the large lesion already described and there were no leiomyomas in the myometrium.



An imprint preparation from the tumor was stained with Wright's stain to obtain better cytologic definition. The cells were medium sized with rather round nuclei which often showed moderate distortion in shape. The nuclei varied moderately in size and had

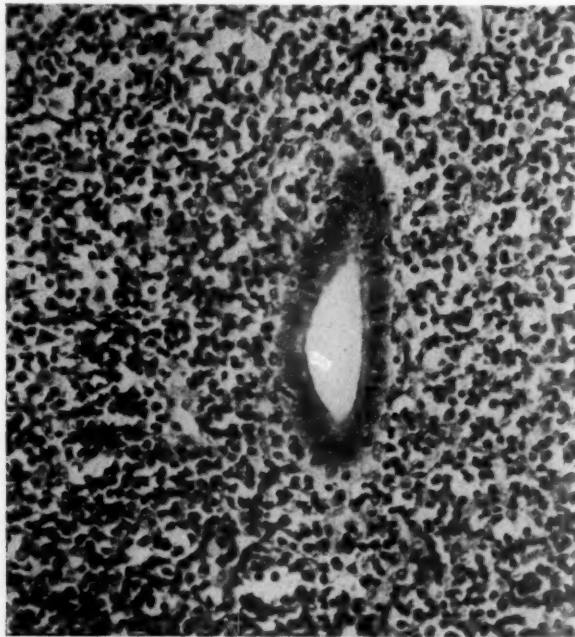


Fig. 2.—Replacement of endometrium by lymphosarcomatous infiltration. Isolated residual endometrial glands. (Hematoxylin and eosin.  $\times 60$ ; reduced  $\frac{1}{4}$ .)

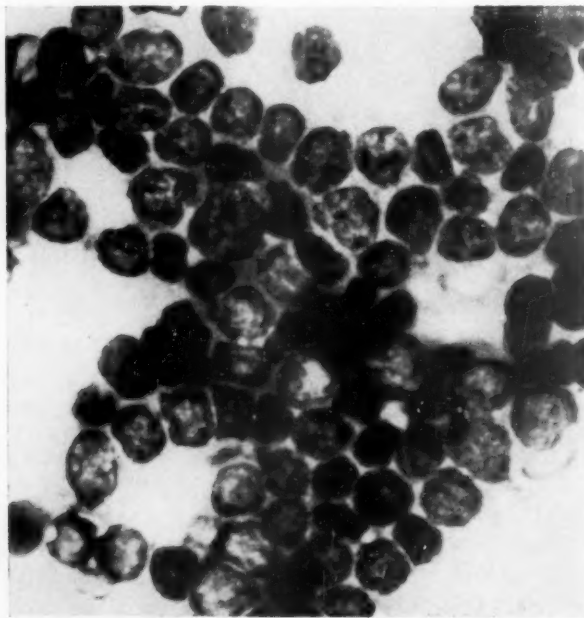


Fig. 3.—Imprint preparation. Moderate distortion of nuclei, scanty cytoplasm, ropelike distribution of chromatin are features of lymphosarcoma. (Wright's stain.  $\times 960$ ; reduced  $\frac{1}{3}$ .)

a coarse ropelike distribution of chromatin. Nucleoli were sometimes seen but were not as prominent as those noted in malignant reticulum cells. The best classification for this lesion on a cytologic basis was considered to be lymphosarcoma using the term in its original sense as suggested by Kundrat<sup>5</sup> (Fig. 3). Sections were compared to the lesion biopsied from the maxillary sinus two years previously. It was apparent that the morphology was similar.

Two months later a similar nodule was removed from the patient's right breast.

### Comment

When the endometrial lesion was available for study it was felt that it represented a sarcoma, probably lymphomatous in character. Endometrial stromal sarcoma can produce lesions of this type but ordinarily the neoplastic stromal cells are oval or spindle shaped and can be recognized on this basis.<sup>6</sup> There may be difficulty, too, in differentiation from some of the leiomyosarcomas of the myometrium which can be characterized by closely packed oval or round cells. It is difficult to know whether any lymphomas may have been included in reports of so-called "round-cell sarcomas" of the myometrium. The predominate localization in the endometrium, as well as absence of evidence of pre-existing leiomyomas, aids in such differentiation.

Our interpretation of the disease in this patient was that she had a lymphosarcoma of the maxillary sinus, a not uncommon form of malignant tumor in this area, with subsequent localization of the lymphoma, first in the endometrium of the uterus and then in stroma of the breast. It seems likely that manifestations will develop in other organs although at the present time there is no evidence of the presence of other lesions. Although lymphocytic lymphomas are prone eventually to terminate as lymphatic leukemia, lymphosarcomas are unlikely to lead to blood stream involvement. Lymphosarcoma of the endometrium appears to be a highly uncommon cause of uterine bleeding if previous reports are any indication. Such a lesion should be kept in mind in evaluation of cases of endometrial stromal sarcoma and cases of "round-cell" sarcoma of the myometrium. The likelihood that it may be only part of a systemic disturbance would mean a more serious implication in such patients.

It seems apparent that the uterus can become involved in malignant lymphoma not only by way of coincidental infiltration during the course of leukemia but also as a part of the manifestations of lymphosarcoma without any actual leukemia. In our case the disease was first manifested by the development of a lesion in the maxillary sinus but from a study of the cases reported by Walther it is apparent that the first symptoms may arise from a uterine lesion. Since lymphosarcomas are not ordinarily associated with involvement of the marrow, blood stream, or spleen, the diagnosis is usually suggested first by examination of the endometrium.

### Summary

Attention is directed to the observation that lymphomatous involvement of the uterus may be a rare cause of uterine bleeding. Such lesions may occur in the absence of manifestations of leukemia and may result in well-localized

bulky lesions. Differentiation from endometrial stromal sarcoma and myometrial sarcoma may be difficult and yet important from the standpoint of implying systemic disease and a more serious prognosis.

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## THE INCIDENCE OF ENDOMETRIOSIS INTERNA IN 120 CASES OF CARCINOMA OF THE ENDOMETRIUM

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RECENT studies of uterine cancer have been concerned with the possible relationships of ovarian stromal-cell hyperplasia,<sup>1, 2</sup> functioning ovarian tumors,<sup>3</sup> and endometrial hyperplasia<sup>4-7</sup> with carcinoma of the uterine body. Considerable evidence has accumulated to make these relationships highly probable and significant. In the routine examination of surgical specimens we have been impressed with the frequency with which uterine endometriosis (endometriosis interna) appeared in conjunction with endometrial carcinoma. To determine whether this frequency is statistically significant was the purpose of this study.

### Review of the Literature

In spite of the relatively frequent studies of endometriosis interna that have appeared in the literature, comparatively little attention had been given to its occurrence in conjunction with carcinoma of the uterus. Several previous reports have noted the frequency of carcinoma in uteri that were the site of endometriosis.<sup>8-13</sup> The results of these studies are summarized in Table I. Only one paper, that of Fahlund and Broders,<sup>14</sup> noted the incidence of sub-basal glands in the uterine wall in an examination of 86 cases of carcinoma of the uterus. They found subbasal glands in 58 of the 86 cases. The term "sub-basal glands" included what we now call superficial endometriosis. Their conclusions in general indicated that the concurrence of the two lesions in the same uterus was probably coincidental and that no causal relationship could be inferred from these studies.

TABLE I. INCIDENCE OF CARCINOMA OF THE ENDOMETRIUM IN ENDOMETRIOSIS OF THE UTERUS (REVIEW OF THE LITERATURE)

AUTHOR	YEAR PUBLISHED	INCIDENCE (%)
Smith, G. V. S.*	1929	7.1
Frankl, O.	1932	2.8
Rockstroh	1936	2.7
Skamnakis	1938	6.0
Fallas and Rosenblum	1940	1.5
Hunter, W. C., et al.	1947	2.1

\*Includes endometriosis interna and externa.

### Materials and Methods

The object of this investigation was threefold: (1) to note the incidence of endometriosis of the uterus in 120 cases of carcinoma of the uterine body;

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(2) to compare this incidence with that of endometriosis in uteri that are free of malignancy; and (3) to consider the significance of these findings, if any, in the light of the other dysfunctional changes and disturbances in growth associated with carcinoma of the endometrium.

The slides of 120 cases of carcinoma of the uterine body were selected from the files of several general hospitals in and around Boston, Massachusetts, and reviewed by the senior author. Cases of carcinosarcoma were not included; neither were cases in which the carcinoma had so invaded the uterine wall that the available slides had little or no myometrium for evaluation. No autopsy material was included. Although the number of blocks available varied from case to case, a minimum of three sections of the uterine body was required, and these sections included endometrium as well as the bulk of the underlying myometrium. In all cases the following were noted: (1) the age of the patient at the time of hysterectomy; (2) the type of carcinoma, its degree of differentiation, and the extent of invasion; (3) the extent of the uterine endometriosis, i.e., minimal, moderate, or extensive. In this study we were concerned only with endometriosis interna, by which we mean the presence of ectopic nonneoplastic endometrial glands with stroma within the myometrium. This definition would include the subbasal or superficial type of endometriosis wherein the glands dip down between the muscle bundles just beneath the endometrial layer. However, we have counted as positive only those cases in which the endometrial glands were well within the uterine wall. This included simple endometriosis as well as the musculoglandular complex termed adenomyosis. In terms of extent, the endometriosis was classified as being present in three degrees: minimal—the presence of at least one focus of endometriosis in the sections available; moderate—the presence of endometriosis in one focus in at least two sections or two separate foci in one section; extensive—any greater occurrence than moderate.

Because a statistical study requires that a comparison is to be made, uteri removed for other reasons than carcinoma were evaluated to determine the incidence of endometriosis interna. These cases, numbering 264, were taken from the same files as were the carcinomas and they were evaluated by the same criteria. Selectivity was performed only to approximate the age distribution of the cancer group. This was done in order to minimize the variable incidence of uterine endometriosis in any given age group. The results were then compared to those of other reports in the literature regarding the incidence of this form of endometriosis in collections of random hysterectomies. This figure does not represent the true incidence in the normal population since most of these patients demonstrated sufficient pelvic disease to warrant hysterectomy. Thus the incidence of endometriosis of the uterus in this control group was expected to be higher than that in the general female population in the same age groups. On the other hand, the uteri containing carcinoma were almost always removed with this diagnosis in mind, so that the incidence of uterine endometriosis in this group was truly incidental.

The mathematics used in evaluating the results were of the simplest type. First, the percentages of uterine endometriosis in both the cancer patients and in the control groups were calculated. Second, the chi-square formula was used to express the likelihood of the results being produced by "chance" distribution of endometriosis in the uteri considered.

### Results

When the 120 cases of carcinoma were placed in consecutive 5 year age groups, we noted that the ages of these patients at the time of operation formed



a distribution curve with the greatest number occurring between ages 55 and 59. Of these 120 cases, 40, or 33 per cent, showed uterine endometriosis. Our control series of 264 cases, when arranged in consecutive 5 year age groups, formed a distribution curve that was fairly similar to that of the carcinoma group, as planned. Of the control series, 48, or 18 per cent, had uterine endometriosis (Fig. 1).

The percentages of endometriosis in each of the consecutive five year age groups was plotted both for the carcinomas and the controls (Fig. 2). The cancer cases in the age groups under 34, 35 to 39, and 40 to 44 were added together so that 56 per cent incidence of endometriosis represented all three age groups. The same was done for the control cases. The percentage incidence of endometriosis interna in the patients with endometrial carcinoma in each 5 year age group was greater than the incidence of endometriosis in the control group with one exception (age 50 to 54) where the percentages were almost reversed. We believe that this and the general irregularity of both curves are due to the relatively small number of cases evaluated in any single 5 year age group. However, the total incidence of uterine endometriosis was 33 per cent in the cancer cases and 18 per cent in the control group.

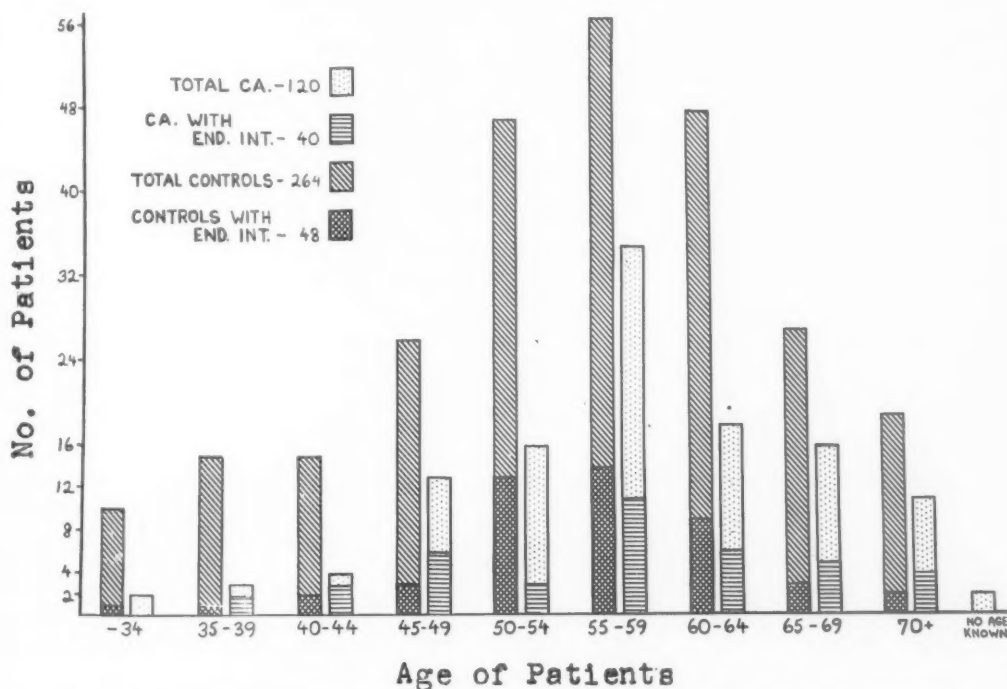


Fig. 1.—Age distribution of endometriosis interna in carcinoma and controls.

These results were sufficiently different to raise several questions regarding other features of the two lesions in the control and cancer series, such as the extent of the endometriosis, the type of tumor, and the degree of differentiation.

1. Was the endometriosis more extensive in patients with carcinoma than in the controls? Table II demonstrates that there was a slightly greater tendency toward a more extensive involvement of the uterus by endometriosis in the cancer cases than in the control group.

TABLE II. THE EXTENT OF UTERINE ENDOMETRIOSIS IN CANCER AND CONTROL CASES

TYPE OF UTERINE ENDOMETRIOSIS	NO. OF PATIENTS WITH CANCER AND UTERINE ENDOMETRIOSIS	PER CENT OF TOTAL PATIENTS WITH CANCER AND UTERINE ENDOMETRIOSIS	NO. OF CONTROLS WITH UTERINE ENDOMETRIOSIS	PER CENT OF TOTAL CONTROLS WITH UTERINE ENDOMETRIOSIS
Extensive	18	45.0	11	23
Moderate	17	42.5	25	52
Minimal	5	12.5	12	25
Total	40	100.0	48	100

2. Does the incidence of endometriosis vary in its occurrence with tumors growing as adenoacanthomas when compared with adenocarcinomas? Table III shows that the incidence of endometriosis is not altered by this quality of the tumor.

TABLE III. COMPARATIVE INCIDENCE OF UTERINE ENDOMETRIOSIS IN ADENOACANTHOMA AND IN ADENOCARCINOMA

TYPE OF CANCER	NO. OF CASES	NO. OF CASES WITH UTERINE ENDOMETRIOSIS	PER CENT WITH UTERINE ENDOMETRIOSIS
Adenoacanthoma	37	12	32.5
Adenocarcinoma	83	28	33.8

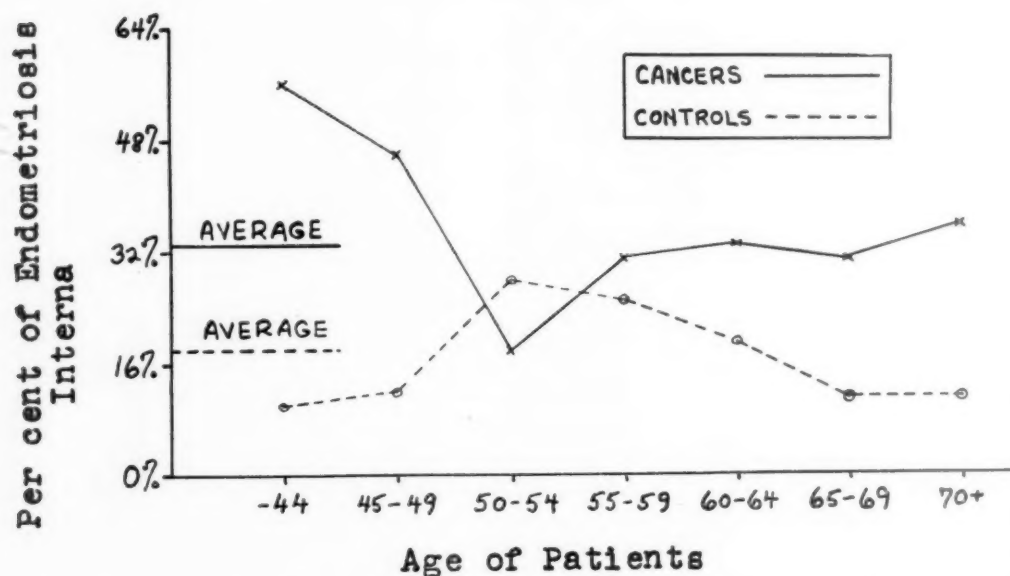


Fig. 2.—Comparative incidence of endometriosis interna in association with carcinoma and in controls.

TABLE IV. COMPARATIVE INCIDENCE OF UTERINE ENDOMETRIOSIS IN WELL-DIFFERENTIATED AND IN POORLY DIFFERENTIATED CARCINOMA

STAGE OF DIFFERENTIATION OF CANCER	TOTAL CASES	NO. WITH UTERINE ENDOMETRIOSIS	PER CENT WITH UTERINE ENDOMETRIOSIS
Well differentiated	91	33	36.3
Poorly differentiated	29	7	24.1
Total	120	40	

3. Does the endometriosis occur more commonly in well-differentiated than in poorly differentiated carcinomas? Table IV shows that endometriosis occurred in 36.3 per cent of the cases when the carcinoma was classified histologically as well differentiated and in 24.1 per cent of the cases when the carcinoma was classified as poorly differentiated.

#### Comment

The incidence of endometriosis in nonselected uteri removed surgically varied from 8.4 per cent<sup>15</sup> to 27.8 per cent<sup>13</sup> in previously reported studies. This variability may have been due to variations in the criteria used for diagnosis as well as other factors. We believe, however, that the 18 per cent incidence of uterine endometriosis in our study, which excluded the more common superficial type, was considerably higher than the incidence in the population at large in the same age groups. Since the endometriosis in the uteri showing carcinoma was entirely a chance finding, we believe that the difference between the cancer group and a truly random control group from the normal population would have been even more striking. Our results, as determined by the chi-square formula, showed a likelihood of duplication by chance of almost one in one thousand (chi-square equals 10.7), and we feel that the likelihood with a more random control group might have been greater.

Furthermore, we have found that the tendency of extensive endometriosis to occur more often in association with the carcinoma than with the control group was significant (chi-square equals 5.99), with a likelihood of chance duplication of about one in twenty. This indicated that not only do carcinoma and endometriosis tend to occur together but also a more extensive type of endometriosis interna is more likely to be found with endometrial carcinoma. The incidence of endometriosis interna did not vary significantly in cases of adenoacanthoma when compared with those of adenocarcinoma. We also found that the difference between the incidence of endometriosis interna in the well-differentiated and the poorly differentiated carcinoma was not significant.

Since this study indicated that the incidence of endometriosis in uteri with carcinoma of the corpus was so much greater than in uteri without carcinoma, it appeared reasonable to postulate that some common factor or relationship existed. This is not to say that this relationship was one of cause and effect, nor do we imply that uterine endometriosis was a predisposing factor in the causation of endometrial carcinoma. Numerous studies have indicated the frequency with which stromal-cell hyperplasia of the ovary, functioning ovarian tumors, and endometrial hyperplasia were associated with endometrial carcinoma. We believe that these are the morphological components of hormonal disturbances. We conclude from this study that the more than incidental association of endometriosis interna in cases of carcinoma of the uterine body places this form of uterine dysplasia among the patterns of pelvic pathology associated with endometrial carcinoma.

#### Summary

1. In a study of 120 uteri containing endometrial carcinoma, 40, or 33 per cent, had endometrial glands well within the myometrium.

2. In a study of a control group comprised of 264 uteri of the same age distribution without carcinoma, removed surgically with a variety of clinical diagnoses, 48, or 18 per cent, showed uterine endometriosis.

3. Application of the chi-square formula indicated that the greater incidence of endometriosis interna in these cases of carcinoma of the uterine body was statistically significant.

4. Extensive endometriosis interna was found more often in the cancer group than in the control group, whereas the incidence of endometriosis did not vary significantly with either the type of carcinoma or its degree of differentiation.

5. The result of this study places endometriosis interna among the disturbances in growth associated with endometrial carcinoma and suggests a possible common etiological background.

We are indebted to Drs. H. E. MacMahon, H. G. Olken, and M. V. MacKenzie for the pathological material used in this study.

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## VAGINAL METASTASES FROM ADENOCARCINOMA OF THE CORPUS UTERI\*

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VAGINAL metastases as a cause of failure in treatment of adenocarcinoma of the endometrium are of clinical interest. This is not only pertinent but practical, for to control this vaginal spread additional treatment techniques and additional effort must be exerted above that required to control the primary disease in the corpus uteri.

Many of the physicians treating this disease make no special effort to treat the vagina prophylactically. Either they do not consider the incidence of vaginal metastasis high enough to warrant the effort, or else they do not think there is an effective routine method of prophylactic treatment. Previous reports indicate that the incidence of vaginal metastases is sufficiently high to cause concern and to justify prophylactic irradiation.

TABLE I. INCIDENCE

AUTHOR	NO. OF CASES		CASES METASTATIC TO VAGINA	%
	CARCINOMA	OF ENDOMETRIUM		
Meigs <sup>1</sup>	206		25	12.1
Way <sup>2</sup>	102		18	17.7
Stander <sup>3</sup>	278		15	5.4
Javert and Douglas <sup>4</sup>	381		40	10.4
Javert <sup>5</sup>	50		5	10.0

Further study of this subject, especially the pathologic anatomy of these metastases, is needed. For example, the mechanism of the spread of corpus carcinoma to the vagina is not clear. Usually we think of the direction of extension as outward and upward; however, in some cases the cervix is involved by direct downward extension from the corpus uteri. In some cases there is a continuous extension from the primary carcinoma; in others this downward spread appears to by-pass the cervix on its way to the vagina. The mechanism and the route of spread of these metastases are not clear. There may be a fascial plane, tissue space, or vascular channel mechanism around the cervix.

The appearance of nodules of carcinoma in the vagina when the disease is first diagnosed and prior to therapy often indicates extensive spread, although the local disease may not be advanced. The visible nodules of carcinoma in the vagina are actually only part of a more generalized metastatic disease. If

\*Presented at the Twenty-eighth Annual Meeting of the Texas Association of Obstetricians and Gynecologists, San Antonio, Texas, Feb. 23, 1957.



the individual shows little resistance to the growth, there may be extensive dissemination of the disease without massive primary growth. The mechanism of spread to the vagina in such cases may be one of retrograde metastasis due to tumor blockage of the pelvic vascular system and tissue spaces, forcing a reversal in flow of the tissue fluids. Finding a metastatic lesion in the vagina in such cases usually warrants a poor prognosis.

The gravity of the presence of a vaginal metastasis on primary examination is illustrated by the following case:

The patient was a 54-year-old white nulligravida, 8 years postmenopausal, with a complaint of slight vaginal bleeding for 2 months. Examination showed an enlarged uterus and a plaque of metastatic adenocarcinoma at the introitus and on the right vaginal wall. The uterine corpus was not greatly enlarged and the parametrium was soft. The endometrium was positive for adenocarcinoma. The patient was treated by heavy pelvic irradiation with the 22-mev. betatron, by the Heyman packing technique, with vaginal radium applicator, followed three weeks later by an abdominal laparotomy which showed metastatic adenocarcinoma in the liver, omentum, and pelvic lymph nodes. The patient appeared in good general physical condition, yet she had extensive metastatic carcinoma.

Vaginal metastases also appear after therapy to the primary tumor. When the metastases are located in the vault, the mechanism may be one of three: (1) Microscopic disease may have been cut through at the time of operation. (2) Fragments of viable tumor which had broken away from the uterine cavity may have been implanted. (3) Viable tumor cells may have been milked, in a retrograde manner, into the lymph or venous vessels of the submucosa or perivaginal tissues. When the metastases are located in the lower third of the vagina, this last mechanism is the most likely.

The rationale of prophylactic radiation treatment is that:

1. The irradiation of the primary tumor in the uterine cavity, if not sterilizing for all tumor cells, damages them and therefore renders them less capable of metastasis by implantation.
2. The irradiation of the vagina with a potentially cancerocidal dose will destroy the microscopic disease and also render the vaginal mucosa less susceptible for a "take." Diminished susceptibility to tumor "take" has been experimentally well demonstrated after irradiation of receiver sites in experimental tumors.
3. The irradiation obliterates potential metastatic channels, reducing the possibility of retrograde implant by milking action when the tumor is handled during operation.

TABLE II. TYPE OF TREATMENT GIVEN PRIOR TO APPEARANCE OF VAGINAL METASTASES

VAGINAL SITE OF METASTASES	NO PREVIOUS TREATMENT	HYSTERECTOMY ONLY	HYSTERECTOMY AND RADIUM TO VAGINA	TOTAL LESIONS
Entire vagina	6	0	0	6
Upper half	3	13	2	18
Lower vagina	2	2	0	4
Rectovaginal septum	1	1	0	2
Posterior wall	0	1	0	1
Introitus	0	3	0	3
Suburethra	3	1	0	4
Total	15	21	2	38

The plan of radiation therapy to the vagina differs whether we are treating prophylactically or for clinically demonstrable metastatic disease. In the first case there are no grossly detectable metastases although they may be present microscopically; if the lesion is small the prophylactic technique will be cancerocidal. Such prophylactic treatment must encompass the entire vaginal vault for metastatic foci may occur at any level. This is illustrated in Table II.

Contrary to the experience commonly expressed, the lower vagina, in particular the suburethral area, was involved in only a small percentage of cases. The incidence is high enough, however, to justify irradiation of the entire vagina.

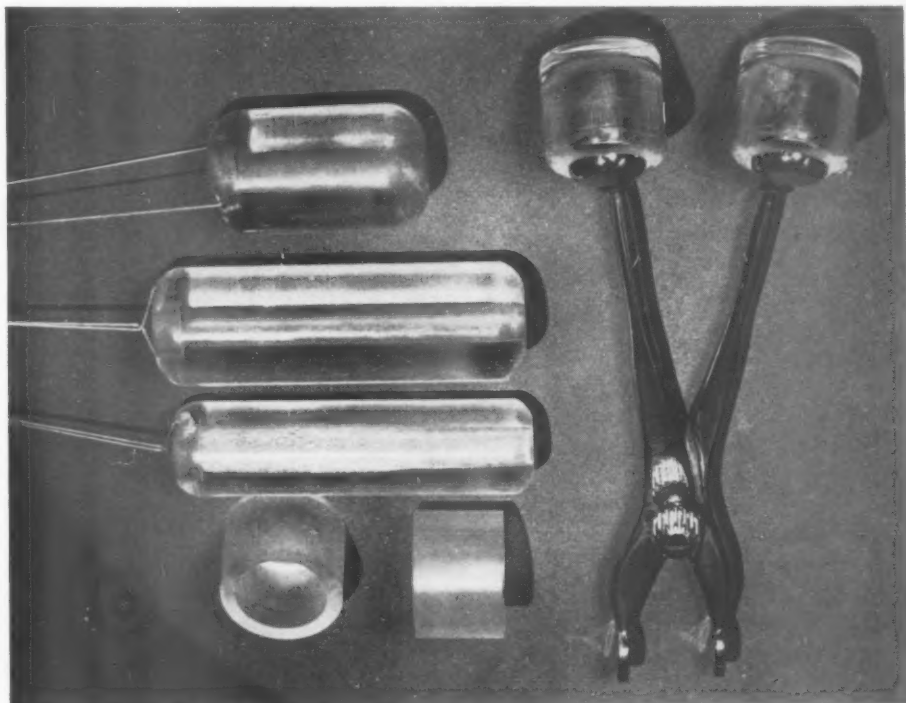


Fig. 1.—To the right are ovoids, with attached handles, that fit into the vaginal fornices and irradiate approximately the upper one-third of the vagina. The distance from the radium source to the vaginal mucosa can be varied by changing the detachable plastic covers on the ovoids. This applicator is used in conjunction with the first radium packing of the uterine corpus.

To the left are three different sized plastic cylinders to hold a linear source of radium. This applicator irradiates the entire vagina and is inserted with the second radium packing of the uterine corpus.

Where there is irradiation of an extensive area such as the entire vagina, the dose must be reduced in intensity at the level of the bladder and rectum to avoid damage to these structures. One can take advantage of the rapid fall-off of the dosage rate of intravaginal radium to deliver a high dose to the vaginal mucosa and submucosa without damaging doses to the rectum and bladder. Because of the high tolerance of the vaginal mucosa, cancerocidal doses of 6,000 to 7,000 gamma r can be delivered without destruction of the vaginal epithelium.

The irradiation technique for the uterine cavity, in this institution, follows very closely the so-called Heyman packing technique. Various sizes of capsules are used, depending upon the size of the uterine cavity, to give an

optimum number of radium sources. The Radiumhemmet tables are used for the length of irradiating time; a second packing is repeated three weeks later. As an average, 3,500 to 4,500 mg. hr. of radium is delivered, which gives an approximate dose of 5,000 gamma r at 2 cm. distal from the endometrium.

Radium therapy of the vagina was carried out until 1952 by using, at the time of the first insertion, Manchester ovoids with radium loading to give a surface dose to the vault of 3,500 gamma r. At the time of the second packing, a vaginal cylinder of maximum length and diameter to reach the entire vagina is inserted (Fig. 1). It is loaded to deliver also a surface dose of 3,500 gamma r. As there is overlapping of the two applicators on the vault and the upper third of the vagina, the mucosa there receives with the two applications a dose of 7,000 gamma r. There is a diminishing mucosal dose downward to the introitus with a minimum of 4,000 to 4,500 gamma r. With this technique there is unhomogenous irradiation of the entire vagina, and, since 1952, a one-piece vaginal applicator has been used (Fig. 2), combining ovoids and cylinder, with a calculated loading to give a dose of 7,000 gamma r to the entire vaginal mucosa. Because of the large amount of radium in this applicator, it is inserted separately a week after the first packing, and usually stays for approximately 4 days.

The incidence of vaginal metastases and complications in the two series will determine which one of the two techniques is best. The first group has now a minimum of 4 years' follow-up.

Second, where there is palpable metastatic disease in the vagina, the irradiation must be more radical and individualized. The depth dose from a vaginal cylinder is too shallow to control larger tumor masses, therefore, external irradiation (preferably supervoltage) is used, transvaginal x-ray, radium needling, and combination therapy, depending upon the location, size, etc., of the tumor. Once there is a metastatic lesion in the vagina, the entire vagina potentially is involved; if there is a chance for a cure one should anticipate these multiple sites and treat the whole vagina initially, otherwise the tolerance of the vagina to radiation is dissipated while one local lesion is being treated, and later the same problem recurs at another level in the vaginal canal. Supervoltage irradiation may prove helpful in these cases, making it possible to irradiate a block of pelvic tissue homogeneously to include most of the vagina.

Two hundred forty-five cases of adenocarcinoma of the corpus uteri were seen at The University of Texas M. D. Anderson Hospital and Tumor Institute from 1944 to July, 1956. Of these, there were vaginal metastases from the corpus lesion in 35 cases (Table III).

TABLE III. ADENOCARCINOMA OF THE CORPUS UTERI, 245 CASES

NO. OF CASES	TREATMENT	VAGINAL METASTASES	
		NO. OF CASES	%
35	None, too advanced	15	8.1
10	Hysterectomy, no vaginal radium	2	20.0
95	Intrauterine and vaginal radium and hysterectomy	2	1.5
44	Intrauterine and vaginal radium, no hysterectomy	0	
184	No previous treatment		
61	Previous hysterectomy, only, when first seen	16*	26.2
245	Total		

\*For treatment see Table V.

The 1.5 per cent incidence of late vaginal metastases in the group of patients (139) who received prophylactic vaginal radium is lower than the literature reports. Of those 139, 42 have a minimum follow-up period of 4 years and the only instance of vaginal metastasis in that group was as part of widespread recurrent pelvic disease. Despite the small number, the statistical significance is real, the upper confidence limit being around 5 per cent.

Our clinical material includes three situations:

1. Cases where there are vaginal metastases as evidence of recurrent disease, but there is also extensive local disease in the pelvis. In such cases the vaginal spread is merely part of uncontrolled disease and has no special interest for this study.

2. Cases presenting vaginal metastases prior to therapy. These are of interest from a prognostic viewpoint, and as an added problem in the therapy of this disease.

3. Cases in which vaginal metastases develop following initial treatment. This group especially interests us for these lesions may be preventable.

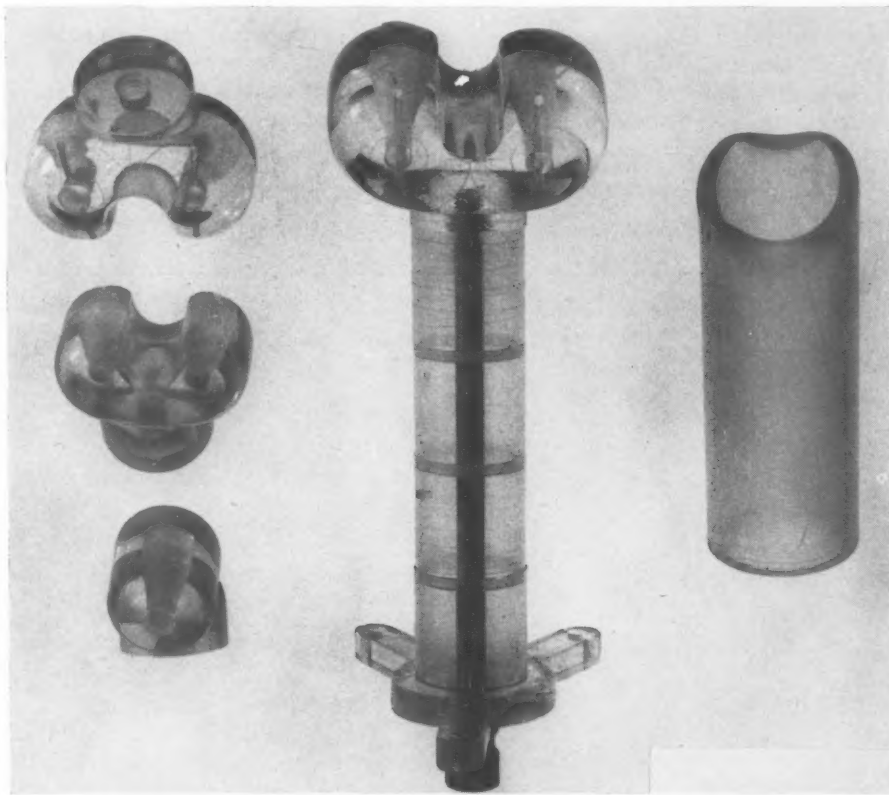


Fig. 2.—This vaginal applicator, designed by Dr. Fernando G. Bloedorn, Chief of Radiotherapy of the University of Maryland Hospital, is a combination of vaginal ovoids and cylinder. The ovoids are detachable so that the proper size can be selected. On the right is a detachable plastic sheath which can be used to increase the diameter of the cylinder. This applicator delivers a more uniform dose to the vagina than the combination in Fig. 1 but its use also requires an additional application time.

In the second situation, Table IV shows the modes of treatment and the results in 15 cases with vaginal metastases without previous therapy to the primary tumor. Many cases were not suitable for treatment and in those that were treated the survival period was short and probably not affected by therapy.



TABLE IV. VAGINAL METASTASES IN 15 PREVIOUSLY UNTREATED PATIENTS

SITE	TREATMENT	SURVIVAL PERIOD
Upper half	Refused	2 months
Whole vagina	0	5 months
Whole vagina	0	18 months
Whole vagina	0	11 months
Suburethra	Cylinder	2 years
Upper half	Cylinder	7 months
Rectovaginal septum	Posterior exenteration	1 year
Suburethra	Ovoids and needles	4 months
Whole vagina	0	Unknown
Middle half	0	Unknown
Whole vagina	0	Unknown
Suburethra	Refused	Unknown
Upper half	Incomplete surgery	Living with disease
Middle half	Betatron	Living 9 months. Bone metastases
Lower half	Beatatron and vaginal applicator	Living 9 months. Metastases to abdomen

In the third situation we had 16 patients sent to the institution with vaginal metastases, who had previously had hysterectomy outside. The plan of therapy in these cases is quite varied because considerable individualization is necessary.

TABLE V. VAGINAL METASTASES IN PATIENTS WITH PRIOR HYSTERECTOMY OUTSIDE

	REASON FOR NO TREATMENT	TREATMENT	SURVIVAL
<i>Not Treated.—</i>			
2	Other local disease in the pelvis		
3	Extensive vaginal disease		
2	Distant metastases		
7			
<i>Treated.—</i>			
2		Vaginal applicator	Still living, 5 years
3		Betatron	Still living, 2 years
1		Radium needle implant	Still living, 2 years
3		Radium needle implant and surgery	One died after 1 year One died after 5 years One living after 4½ years
9			

Among the treated patients, 3 have had recurrent disease several times within a 4 year period, despite both radium needle implant and operation. It can be noted that therapy offers some worth-while control of the local metastases.



The majority of vaginal metastases will appear within the first year after therapy to the primary tumor. It is not possible to determine at what stage of the uterine disease vaginal metastases occur. One would expect them to parallel the extent of the disease at the primary site. However, we do not know that this is the case nor is it possible to determine, prior to hysterectomy, the degree of involvement of the corpus. Therefore, we feel all cases should have prophylactic vaginal radiation.

TABLE VI. TIME OF APPEARANCE OF METASTATIC LESIONS FOLLOWING THERAPY

Present prior to treatment	15
Within 1 year	13
Within 2 years	2
Within 3 years	3
Within 6 to 8 years	2

### Summary

In 245 cases of adenocarcinoma of the corpus uteri seen, 35 cases showed disease in the vagina. These vaginal metastatic lesions were present in 15 cases when the patients were first seen, without prior treatment. In the remaining 20 who had previous treatment, 16 had had hysterectomy outside; 2 had hysterectomy in this institution without radium therapy to the vagina, out of a group of 10 so treated; and 2 out of a group of 139 treated with radium, 95 of whom had a hysterectomy also. Forty-two patients have a minimum of 4 years' follow-up.

Because of the fact that the majority of vaginal metastases appear within one year and also that 42 cases have been followed for 4 years, the 1.5 per cent incidence, compared with that given in other reports, seems to point to the effectiveness of prophylactic radium therapy to the uterus and vagina. This justifies carrying out such prophylactic irradiation. Longer follow-up will determine how low this incidence will stay.

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### Discussion

DR. WILLIS H. JONDAHL, Harlingen, Texas.—Dr. Rutledge has presented a very interesting paper on a subject that has had scant attention in the literature.

The fact that from 5.4 to 17.7 per cent in various series of cases of endometrial carcinoma showed vaginal metastasis makes it clinically important that more attention be given to this complication.

The mechanism of spread is not always clear but the appearance of tumor nodules in the vagina prior to therapy often indicates extensive spread of the primary tumor to distant parts of the pelvis by blockage of the pelvic vascular system and tissue spaces, giving a retrograde metastasis. The prognosis in these cases is usually poor.

Many of the vaginal metastases appear later after therapy has been given. These may be related to the treatment procedure where fragments of viable tumor are implanted in

the surgical cuff, or are milked into the vaginal spaces, venous or lymph channels at the time of operation. It is in this latter group that irradiation of the vagina can improve results.

The Bloedorn applicator is an ingenious device that allows a high level, shallow dose to be given to the entire vagina and yet gives reduced intensity at the level of the bladder and rectum, to avoid destruction of these structures. The applicator is of course useful only in the prophylactic group as much more radical treatment must be given by external or transvaginal x-ray, or radium needling, if palpable disease is present at the beginning of therapy. It is also important to remember that sites of metastases can be multiple and therefore the entire vagina should be treated and not just the local area.

The incidence of complications following irradiation of the vagina is high and should be kept in mind before the procedure is advocated as routine in all cases. If carcinoma is present in the vagina, however, it is imperative that an attempt be made to save the patient's life, and if fistulas or radionecrosis occur they can be treated later if the patient survives.

The complications that occurred in the prophylactic group all seemed to be related to the applicator's not staying in place and further methods are being developed to aid in its support.

## ENDOMETRIAL ADENOCARCINOMA ELEVEN YEARS AFTER PELVIC RADIATION FOR CERVICAL EPIDERMOID CARCINOMA

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ALTHOUGH reports of concomitant pelvic malignancies of differing histologic patterns are not unusual in the literature, there have been few reported cases in which adenocarcinoma of the endometrium followed by more than a decade adequate pelvic radiotherapy for cervical epidermoid carcinoma. Zuspan<sup>1</sup> reported such a case in which the appearance followed therapy by 14 years, and Fernandez-Colmeiro<sup>2</sup> encountered 3 more cases in which adenocarcinoma appeared more than 10 years after satisfactory therapy of carcinoma of the cervix with radium. Fricke<sup>3</sup> has reported 2 other such cases, and a third in which the appearance of adenocarcinoma followed the initial therapy by 9 years, but the original slides could not be obtained for confirmation of the primary lesion. The present case is of particular interest in that it presents not only the appearance of endometrial adenocarcinoma 11 years after the successful therapy with radium of carcinoma of the cervix, but also in that it demonstrates the appearance and progression of adenomatous cystic hyperplasia of the endometrium despite massive doses of pelvic radiation.

### Case History

C. S., a 68-year-old married nulliparous woman, was admitted to our Health Center through the Columbus Cancer Clinic in January, 1956, with a chief complaint of vaginal bleeding of 2 months' duration. The patient had previously been admitted in 1954 and 1955 for unrelated complaints, and had been well otherwise for 9 years.

*Past History.*—She had had a breast biopsy for a benign lesion in 1930, and in 1936, at the age of 48, had had a right oophorectomy and appendectomy at another hospital.

In May, 1944, biopsy was taken of a lesion of the external cervical os at another hospital, and a diagnosis of epithelioma of the cervix, Grade III, was established. On clinical evaluation at that time there was thought to be parametrial involvement with tumor to the lateral pelvic wall, and the case was classified as Stage III. The chief complaint at that time was postmenopausal spotting. Initial therapy consisted of 3,600 mg. hr. of radium by tandem applicator (50 mg. for 72 hours). In October of the same year, for completion of therapy, intravaginal x-ray of 4,800 r (800 r 6 times) was carried out. The patient was followed in the outpatient department of that hospital at intervals and apparently remained well except for occasional hot flushes until March, 1947. At that time the patient again noted vaginal spotting, and on examination there was clinical evidence of recurrence locally without parametrial involvement. Biopsy of the lesion of the cervix and curettage of the uterus were carried out. Frozen section from the cervix was reported epithelioma, Grade III. Confirmation of this diagnosis could not be made on the

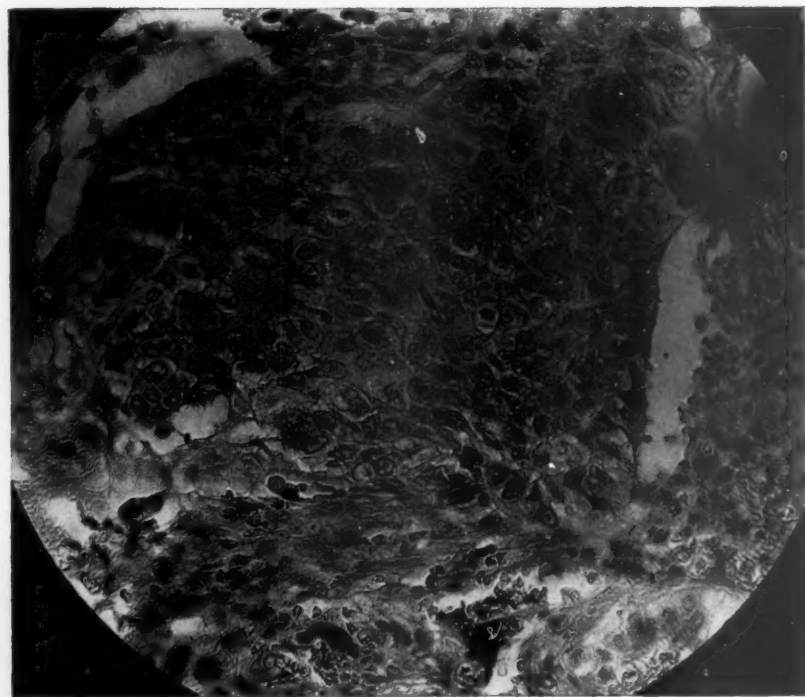


Fig. 1.

Fig. 1.—Appearance of the original epidermoid carcinoma of the cervix at the time of biopsy in 1944.

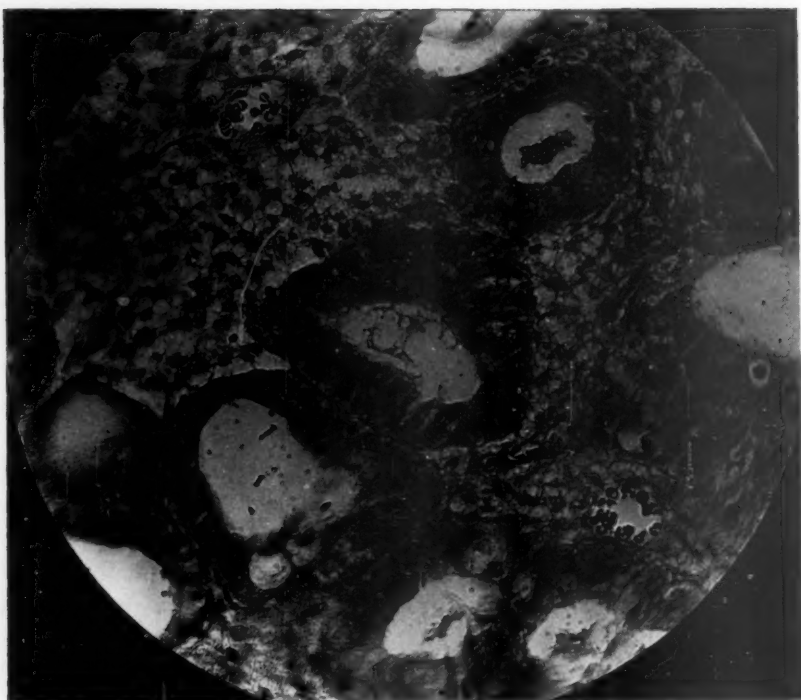


Fig. 2.

Fig. 2.—Endometrial curettings taken at the time of recurrence of carcinoma of the cervix (1947) showing adenomatous cystic hyperplasia of the endometrium.

remainder of the tissue for fixed specimen, and the supplementary report showed cervicitis and adenomatous cystic hyperplasia of the endometrium. The patient was treated with external pelvic radiation of 3,600 r by alternating 300 r to the anterior and posterior pelvis for 12 treatments. Four months later she was given 168 hours of radium with two No. 4, one No. 3, and nine No. 2 needles. It is impossible to determine the exact dosage that this represented in milligram hours of radium.

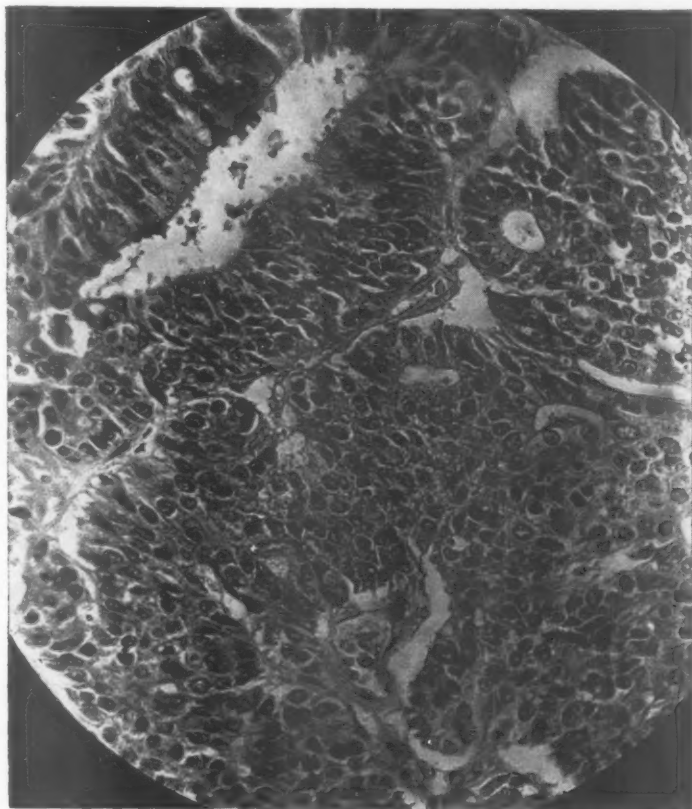


Fig. 3.—Biopsy of adenocarcinoma of the endometrium obtained at the time of admission to the Ohio State University Hospital in January, 1956.

The patient remained well following this therapy except for recurring hot flushes until the time of her first University Hospital admission for fracture of the right ankle in 1954. Pelvic examination done at the time of that admission is recorded as showing no disease. The previous therapy for carcinoma of the cervix was noted on the chart, but Papanicolaou smear was not done at the time of that admission. Pelvic examination was again normal on readmission in 1955 for removal of a screw from the right ankle.

The patient was treated later in the year 1955 for her continuing hot flushes by her local physician with "hormones" for a period of several months. At the termination of therapy, the patient noted the onset of vaginal spotting which she considered to be insignificant at first. After continuation of the spotting for 2 months, the patient visited the Columbus Cancer Clinic, and examination at that time showed the fundus to be somewhat enlarged and displaced to the right. There was thought to be some thickening of the left uterosacral ligament. The patient was referred to the University Hospital for admission.

*Physical Examination.*—The blood pressure was 130/80, and the pulse regular. The patient was well developed, and within the ideal weight range for her height and age.



The pelvic examination substantiated the findings in the Columbus Cancer Clinic. There was scant dark blood coming from the cervical os, but no gross lesion of the cervix was identifiable.

*Hospital Course.*—Biopsy of the cervix and dilatation and curettage of the uterus were carried out without difficulty. Pelvic examination under anesthesia again confirmed the previous findings. On curettage a moderate amount of friable material was obtained which was reported as moderately well-differentiated carcinoma of the endometrium. Specimens of cervix demonstrated only fibrosis and cervicitis.

Because of the history of moderately heavy radiation for the original tumor, and inasmuch as the exact dosage could not be determined, it was thought that further therapy with cobalt<sup>60</sup> should be avoided. The patient was treated with radical hysterectomy with wide excision of the vaginal cuff, and left salpingo-oophorectomy. Because of radiation fibrosis in the pelvis, extensive lymph node dissection was not attempted. The postoperative course was uneventful, and in February, 1956, after 2 weeks' hospitalization, the patient was discharged.

She has been followed since operation in the outpatient department of the Columbus Cancer Clinic, and her most recent admission to the hospital was in December, 1956, 10 months following operation. An inoperable recurrence of moderately well-differentiated adenocarcinoma was noted in the vaginal vault at that time. This was treated with a palliative cobalt<sup>60</sup> mold in the vagina, which delivered approximately 5,000 r to the vaginal mucosa at the area of tumor, 680 mg. hr. radium equivalent.

### Comment

The appearance of this second primary tumor of the uterus 11 years after the treatment of the original neoplasm prompts speculation on origin; whether this development is through stimulation by radiation as postulated by some,<sup>4, 5</sup> or through the probability that any patient may develop a primary neoplasm of an organ. Certainly the higher incidence of carcinoma of the endometrium appearing years after the application of small doses of radiation to the pelvis is well recognized,<sup>6</sup> but it is unlikely that the massive amount of radiation given in this case would act to stimulate the one remaining ovary to the production of excessive amounts of estrogens, this being the usual hypothesis advanced in explanation of the carcinogenic activity of smaller doses of radiation.

Although there is apparently no common causal relationship between carcinoma of the cervix and endometrial hyperplasia,<sup>7</sup> it is of further interest that these two conditions were demonstrated to be coexistent at the time of recurrence of cervical carcinoma in 1947. In spite of the high local radiation at that time, the course of progression from adenomatous hyperplasia to carcinoma was not arrested. Others<sup>8</sup> have made this observation, utilizing smaller amounts of radiation therapy, but there are no other reported cases in which a proved hyperplasia has been subjected to this amount of radiation (even though through secondary intention) and has been followed as in the present case to an eventual termination in frank adenocarcinoma. This certainly seems to militate strongly against the treatment of adenomatous hyperplasia of the endometrium with radiation, even though the use of strontium<sup>90</sup> beta rays has been attempted by some investigators<sup>9</sup> very recently and abandoned only because of the technical difficulties in its management.

It is possible that some degree of endometrial hyperplasia may have been present even at the time of the original cervical biopsy, and, in the light of

present knowledge, the course of therapy might have been altered by such a factor. Dilatation and curettage of the uterus should be carried out whenever technically possible prior to the institution of therapy, even in the presence of obvious exophytic lesions of the cervix.

### Summary

1. A case of adenocarcinoma of the endometrium which developed 11 years after radiation therapy for squamous-cell carcinoma of the cervix is presented.
2. Progression from adenomatous hyperplasia of the endometrium to adenocarcinoma of the endometrium was not arrested by cancerocidal levels of radiation to the uterine cervix.
3. The role of radiation in the stimulation of endometrial carcinoma is briefly discussed.
4. Radiation as a treatment for adenomatous hyperplasia of the endometrium should be discouraged.

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# PRIMARY SARCOMA OF THE FALLOPIAN TUBE

## Review of the Literature and Report of One Case

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IN 1886, Emil Senger<sup>1</sup> reported the first case of primary sarcoma of the Fallopian tube. In 1946, Scheffey, Lang, and Nugent<sup>2</sup> found 21 cases reported in the literature and added the twenty-second case. Eight additional cases have been reported. Recently a patient with primary sarcoma of the Fallopian tube was referred to the private service of Dr. John B. Montgomery. In view of the rarity of this lesion a review of the literature (through September of 1956) and a case report were in order (Table I).

TABLE I. REVIEW OF THE LITERATURE

AUTHOR	AGE	OPERATION	DIAGNOSIS	FOLLOW-UP
Grisi <sup>3</sup>	51	Bilateral "adnexectomy"	Fusicellular sarcoma, left tube	None
Leuret <sup>4</sup>	None	Hysterectomy, bilateral salpingo-oophorectomy	Fusiform sarcoma, right tube	Died in 7 weeks
De Giosue and Lenzi <sup>5</sup>	62	Subtotal hysterectomy, bilateral salpingo-oophorectomy	Unilateral reticulosarcoma	None
Cabrera and Guzman <sup>6</sup>	59	Bilateral salpingo-oophorectomy	Sarcoma, right tube	Died in 7 months <sup>7</sup>
Von Falge <sup>8</sup>	51	Hysterectomy, bilateral salpingo-oophorectomy	Sarcoma, right tube	None
Bornstein <sup>9</sup>	49	Subtotal hysterectomy, salpingo-oophorectomy	Leiomyosarcoma (unilateral)	Died in 1 year <sup>10</sup>
Astorri <sup>11</sup>	25	Left salpingo-oophorectomy	Reticulosarcoma, left tube	Parturition in 1 year
Zorzi and Callegari <sup>12</sup>	23	Hysterectomy, bilateral salpingo-oophorectomy	Leiomyoblastoma, left tube	Died in 2 years

The following case history represents the thirty-first case of primary sarcoma of the Fallopian tube.

On Feb. 11, 1952, Mrs. M. M., 21-year-old gravida ii, para i, underwent a cesarean section, performed by Dr. Andrew Klembara of Pottsville, Pennsylvania. A mass excised from the ampulla of the right Fallopian tube was diagnosed as a primary sarcoma (Fig. 1). The patient was referred to the private service of Dr. John B. Montgomery for further definitive treatment and was admitted to the Jefferson Medical College Hospital on April 27, 1952. The original tissues were reblocked and restained, and the histologic report gave the following information:

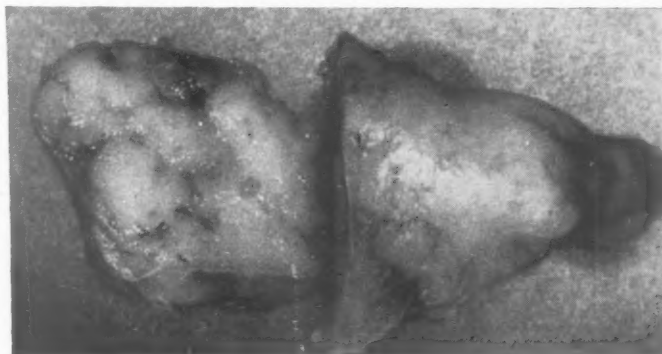


Fig. 1.—Gross specimen of portion of right Fallopian tube, an irregular ovoid mass, measuring 3.5 cm. in length. External surface on right, smooth, shiny, and tan. Cut surface on left, lobulated, grayish white, and moderately firm in consistency.

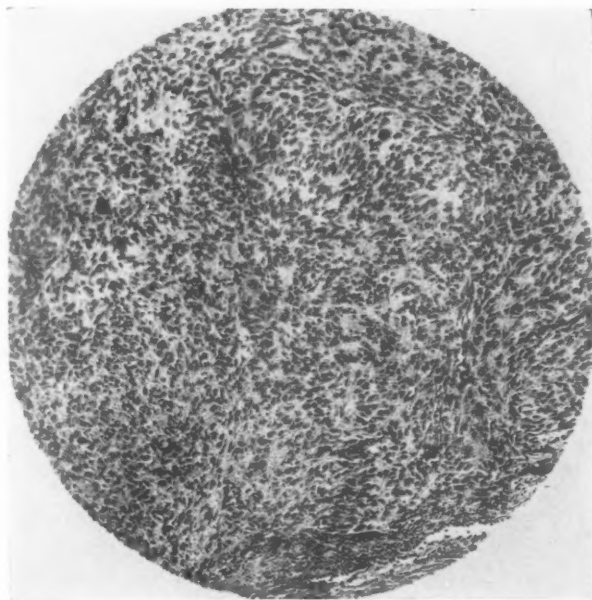


Fig. 2.—Photomicrograph of leiomyosarcoma of right Fallopian tube. The tumor cells are arranged in poorly defined bundles which run haphazardly in all directions. (Hematoxylin and eosin;  $\times 100$ .)

Hematoxylin and eosin sections showed a rather uniform compact cellular mass delineated by a thin but definite connective tissue capsule. The tumor cells were arranged in poorly defined bundles which ran haphazardly in all directions. Their pattern was interrupted only by a moderate number of scattered dilated vessels and an occasional collagenous band extending in from the capsule. The individual cells were spindle shaped with eosinophilic cytoplasm usually not sharply demarcated. The cells ran parallel to one

another but there was no palisading. The nuclei were generally large, oval, sharply demarcated, and finely stippled with chromatin; they varied in size, however, with round, lobulated, and irregular forms. There were moderate variation in size and less variation in intensity of staining. Several mitotic figures were seen per high-power field (Fig. 2). With van Gieson stain the cytoplasm of the tumor stained yellow, indicating the myomatous nature of the lesion. The stain also demonstrated the paucity of stroma within the tumor.

*Pathologic Diagnosis.*—Leiomyosarcoma of the right Fallopian tube.

Urinalysis, complete blood count, and erythrocyte sedimentation rate were all within normal limits with the exception of a mild normochromic anemia. The patient was transfused with one unit of whole blood and on May 6, 1952, underwent a wide total hysterectomy, bilateral salpingo-oophorectomy, and excision of a small portion of omentum that was adherent to the uterine fundus. Preliminary palpation of the liver and exploration of the abdomen and pelvis suggested no metastases. Histologic examination of the surgical specimens revealed no evidence of malignancy, the entire lesion having been removed by the original local excision. The postoperative course was uneventful and the patient was discharged in good condition two weeks later. She has continued to enjoy good health. A thorough examination performed in January of 1957 failed to disclose any evidence of suggestion of metastatic disease or local recurrence.

### Comment

This patient is the youngest reported to have had primary sarcoma of the Fallopian tube. Guercio<sup>13</sup> reported one case of sarcomatous reticuloendothelioma of the Fallopian tube, and Ferrando<sup>14</sup> reported one case of primary carcinosarcoma; it was decided merely to mention these 2 cases rather than to include them in this report. The clinical and pathologic aspects of this rare lesion have been thoroughly explained by Scheffey, Lang, and Nugent.<sup>2</sup>

### Summary

Thirty cases of primary sarcoma of the Fallopian tube have been reported in the literature. An additional case of primary leiomyosarcoma of the right Fallopian tube in a 21-year-old secundigravida has been presented.

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## CARCINOMA PRIMARY IN BARTHOLIN'S GLAND\*

### Case Report

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WHILE pelvic malignancy occurred in 3.5 per cent of all gynecological admissions to the Woman's Hospital, only 1.8 per cent of these cancers were primary in the vulva, compared to the 3 to 4 per cent reported in the literature.

Carcinoma primary in the gland of Bartholin or its duct is even more rare, accounting for 9, or 6.5 per cent, of Taussig's<sup>5</sup> 138 cases, and only 17, or 1.8 per cent, of 940 vulvar malignancies collected by Parrott and Miller.<sup>4</sup> No such primary case was operated upon at the Woman's Hospital in the 27 years prior to 1956.

L. T., No. 127565, aged 55, divorced, gravida iii, para iii, was first seen Jan. 25, 1956, complaining of intermittent vaginal bleeding of 4 months' duration. Other symptoms were itching and burning inside the introitus on the left side at infrequent intervals for several years.

Menses were normal until the menopause in 1952, three years before onset of the current spotting. There was no venereal or specific infection.

The obstetrical history included a traumatic breech extraction with perineal repair. The second and third confinements were without incident and all three children survive.

Although examination following the last confinement in 1931 was said to be normal, since then the patient had noted soreness or itching in the left vaginal region at long intervals, not requiring treatment. There was no dyspareunia.

Of interest in connection with physical findings on admission was a fall in 1951 when the patient struck the right groin against her sewing machine.

Examination showed a well-nourished woman, 5 feet, 1 inch tall, weighing 130 pounds. In the right groin was a tender, partly mobile lymph node about 4 cm. in diameter. Otherwise, cervical, axillary, and inguinal nodes were not unusual.

Pelvic examination showed a deep laceration of the perineum with a thin mucomucous bridge, and a small rectocele. Just inside the hymeneal ring was a dull red, partly ulcerated lesion on the left posterolateral vaginal wall corresponding to the site of the orifice of the duct of Bartholin's gland, with an irregular border and a diameter of 2.5 cm. This was continuous with a wedge of induration extending some 6 cm. into the left ischiorectal fossa and nearly to the periphery of the external sphincter ani, but nowhere near the ischiopubic ramus.

The rest of the vaginal walls were not involved. The cervix presented a tiny cyst, and the corpus was in second-degree adherent retroversion. Otherwise no palpable abnormality was noted in it or the adnexa. Rectal examination disclosed no enlarged sacral nodes or intrinsic lesion.

\*Presented at a meeting of the New York Obstetrical Society, March 12, 1957.

On admission the temperature, blood, and urine were normal. X-rays of the lungs, long bones, and pelvis were normal, while only arthritic changes appeared in the lower spine. The Wassermann test was negative.

Examination under anesthesia on Jan. 31, 1956, confirmed the previous findings.

To rule out a downgrowth from the uterus or cervix a fractional curettage preceded the biopsy and coagulation of the lesion in the left vaginal sulcus. The curettings revealed atrophic endometrium and chronic endocervicitis with scarring. Sections from the vaginal lesion showed partly epidermoid and partly transitional-cell carcinoma with some plexiform and some adenoid patterns. The pathologist, Dr. Motyloff, drew attention to a possible origin of the carcinoma from the left Bartholin duct.

Radical vulvectomy and lymphadenectomy were planned and the first stage was performed on February 4. The inner vulvectomy incision included an inverted V-shaped segment of the left vaginal wall extending up to the cervix and incorporating a 1.5 to 2 cm. uninvolved margin around the growth. The outer incision was wider on the left side and included the entire perineal bridge and a portion of the sphincter ani muscle in order to excise deeply the tongue-like prolongation of growth into the left ischiorectal fossa.

Recovery was complicated by fecal incontinence which steadily improved in 2 weeks, and the patient was discharged on the twenty-first day. The deep perineal and ischiorectal wounds filled in slowly, delaying the second stage for about two months.

On April 18, 1956, bilateral lymphadenectomy was performed, including the superficial and deep femoral and inguinal, external and common iliac groups. Both obturator and hypogastric regions were explored but only partially cleared. It is noteworthy that, while the ipsilateral nodes showed no cancer, a metastasis was demonstrated in the contralateral enlarged inguinal node.

After profuse drainage both wounds slowly granulated, and the patient left the hospital May 26. Bilateral sinuses persisted while several silk sutures from the Bassini-type repair sloughed out.

*Interim Result.*—When last seen, Feb. 26, 1957, 13 months after the first operation, the patient was well, back at work as a librarian, and had no evidence of recurrence.

*Pathological Examination* (from the report by Dr. Leon Motyloff).—The vulva, removed en bloc with perineum, ischiorectal fat, and part of the vagina, showed the lesion of the left vaginal wall and fourchette bearing a crater 1.5 cm. in diameter and 0.5 cm. deep. Subjacent induration of the vaginal wall for 1.5 cm. was continuous with a wedge of thickened ischiorectal tissue.

Microscopic sections showed partly transitional epidermoid plexiform carcinoma associated with a solid tubular glandular growth closely related to adjacent lobules of Bartholin's gland. The latter showed chronic inflammatory infiltration, involutional changes, and occasional cystic distention of the lobular ducts near the carcinoma, which apparently involved the main duct of the gland. The solid tubular elements of the carcinoma imitated the structure of the tubules of the Bartholin gland (Figs. 1 and 2).

The depth of infiltration of the malignant cells reached 7 mm. in some areas, but there was no evidence of invasion of the ischiorectal fat beyond the main lesion, which was apparently confined to the site of the left Bartholin gland. Inflammatory infiltration of the entire ischiorectal tissue extended down to the fragments of sphincter ani muscle.

Study of tissues removed at bilateral lymphadenectomy showed on the left (ipsilateral) side 8 superficial and 3 deep nodes with chronic lymphadenitis but with no evidence of metastasis. On the right (contralateral) side a large superficial inguinal node measuring 4 by 2 cm. showed epidermoid partly transitional-cell carcinoma with glandular pattern in some areas, and with calcification and psammoma bodies. One smaller superficial node showed extensive hilar metastases. In summary, the metastatic carcinoma was found only in the superficial inguinal nodes of the side opposite the primary lesion.

Fig. 1.

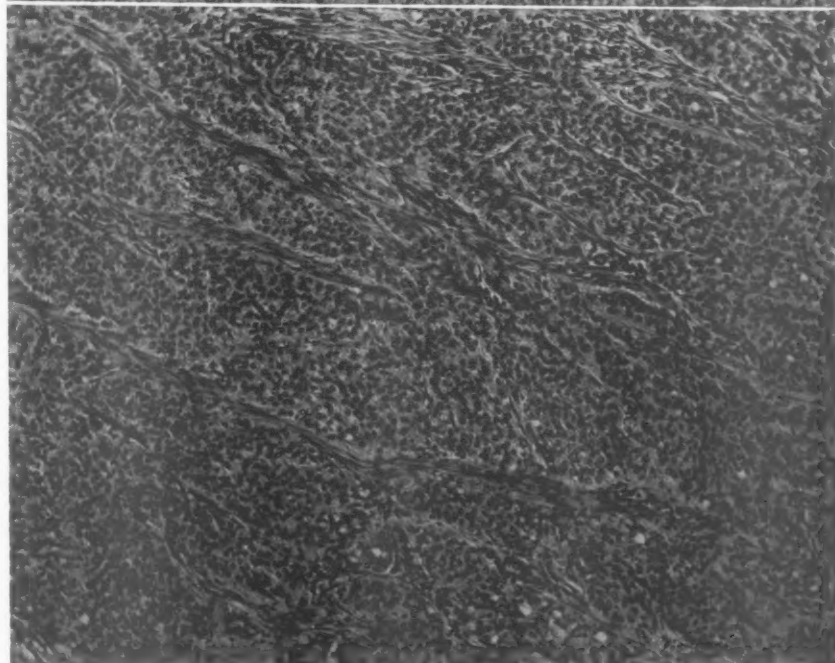
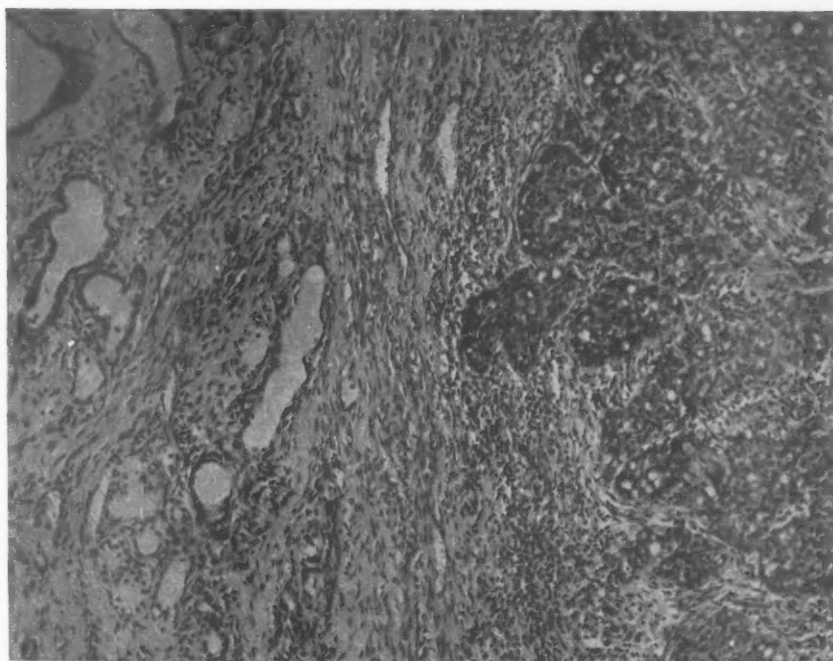


Fig. 2.

Fig. 1.—Bartholin's gland, showing carcinoma in apposition to lobules of the gland.

Fig. 2.—Partly epidermoid, partly transitional-cell carcinoma with solid tubular patterns.

### Summary and Conclusions

1. A case of carcinoma occupying the region of the left gland of Bartholin and its duct is reported. Its origin from that gland is indicated by its location,

by the presence of transitional-cell differentiation, solid tubular or adenoid patterns, all repeated in the regional lymph node metastasis, and by the absence of demonstrable malignancy elsewhere.

2. Possible etiological factors are obstetric trauma, chronic inflammation in the neighboring vulvar and ischiorectal tissues, and involutional and cystic changes in the lobules of Bartholin's gland. In 3 of Taussig's 6 cases there was a history of previous Bartholin cyst. The implications for prophylaxis are obvious.

3. As to prognosis, favorable factors are the absence of tissue permeation beyond the main lesion, the negative clinical and histological findings in the deep iliac and obturator regions, and the apparent lack of recurrence in the first 13 months. Nevertheless, the long history, insidious onset, and contralateral superficial lymph node metastases make the long-range outlook rather doubtful, in conformity with the poor results reported in the literature.

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### Discussion

DR. FRANK R. SMITH.—The incidence of vulval cancer is generally regarded as being about 4 per cent of all genital cancer. At Memorial Hospital where we have had about 435 patients with cancer of the vulva, I think there have been no more than 8 patients with cancer of Bartholin's gland, a very low incidence.

In his last book, Dr. Emil Novak stated that 90 per cent of Bartholin's gland carcinomas are adenocarcinomas and the other 10 per cent are epidermoid carcinomas. The epidermoid type causes some confusion because it may be hard to determine whether such a case has its origin as a primary cancer of the anus or of Bartholin's gland.

At Memorial Hospital, we have thought that adenocarcinoma of the Bartholin's gland did not behave exactly like the other carcinomas of the vulva, but behaved like other adenocarcinomas in that distant metastases resulted. This was based on the fact that one patient in 4 had distant metastases. Perhaps we often confuse primary cancer of Bartholin's gland with a secondary cancer.

We have 2 patients with carcinoma of Bartholin's gland in our "alive" files whereas there are about 135 patients who had had cancer of the vulva during the years 1926 to 1952 who survive and are free of disease.

DR. GRAY H. TWOMBLY.—I think the thing that should be emphasized in this case presentation is the rarity of this lesion. I have seen only one in my experience and I believe in the files at Bellevue Hospital there are only 2.

One case that I saw had been treated with radiation therapy and proved to be exceedingly radioresistant. So, judging from that very infinitesimal experience, I would say that this is a surgical problem.



We have had 2 recent cases that were thought by various observers to be primary carcinoma of the Bartholin gland. They proved to be metastatic disease, in the first case a metastasis from a hydronephroma, the second a metastasis from a chorionepithelioma.

These cases aroused considerable interest on the service, so we have been looking up some of the literature on the subject. There is a good review article in the *Obstetrical and Gynecological Survey* of 1951 by Wharton and Everett, in which they were able to collect only 109 cases in the entire world literature, which emphasized again the rarity of this disease.

In Dr. Sackett's case there was a crossed metastasis, that is, the nodes on the same side as the tumor were not involved but those on the opposite side were. A few years ago we had occasion to put some radioactive gold underneath a carcinoma of the vulva and then do a radical vulvectomy and bilateral groin dissection in continuity. The whole specimen was fixed and cleared. This gave us a most interesting demonstration, because the lymphatics from the vulva were outlined by the radioactive gold and appeared as pale, dove-gray lines lying very deep in the tissue right on the deep fascia. The profusion of these lymphatics was really quite striking. There were hundreds of them coming up over the mons. The other thing that was enlightening was that, when the radioactive gold was put in on one side, radioactivity was found promptly not only in the nodes on the same side but also on the opposite side. In other words, there was a free anastomosis of lymphatics. Evidently anything passing up the lymphatic channels would go either to one side or the other quite freely.

Dr. Sackett stated that the groin dissection drained for a long time. Recently we have been experimenting with the possibility of reducing this drainage time and the necrosis that so often occurs in groin dissections by putting catheters with many holes cut in the ends of them under the skin flap of the groin dissections and connecting them with suction, an idea taken from radical breast surgery. The most recent case we have tried this out in has given a beautiful result. There was no necrosis, but prompt adhesion of skin flaps, so there was really no collection of serum at all under the skin flaps. I think it is a method that might well be taken into consideration by other members of this Society.

DR. MICHAEL J. JORDAN.—I would like to present a case of a patient with carcinoma of Bartholin's gland who was operated on yesterday. She was seen for the first time 10 weeks ago and at that time she presented a lesion involving the right Bartholin gland with ulceration. There were large fixed nodes in both groins, measuring anywhere from 2.5 to 4 cm. The nodes in the left groin were subjected to biopsy and showed essentially the same pattern as the primary lesion itself, which was a mixture of adenocarcinoma and anaplastic epidermoid carcinoma.

It was decided at that time to try this patient on some million volt rotating therapy and she was given a total of approximately 4,000 r units tumor dose to the primary lesion and approximately 2,000 to each groin. This patient returned to Memorial Hospital last Saturday. The primary lesion and the fixed nodes had completely disappeared. In view of this it was decided to do an exploratory operation. At the time of this operation, which was done yesterday, a total hysterectomy was performed because of the presence of fibroids, and at the same time a dissection of the pelvic lymph nodes bilaterally down to the external ring was carried out. A bilateral groin dissection, superficial and deep, was done. The pelvic nodes present were small and grossly negative, and the specimen in general showed no gross evidence of disease.

There is a small amount of thickening in the right Bartholin gland which was not removed at this time. If one were making an examination for the first time, one would think perhaps that there had been a mild inflammation of the gland at some time.

Some of these cases are therefore particularly radiation sensitive. This was not at first a case that would justify surgery and yet 10 weeks later the patient is without any apparent disease. If all specimens taken yesterday come back negative, I intend to remove the vulva, to see if there is any residual disease in the right Bartholin gland itself.



DR. JOHN G. MASTERSON.—I became interested in the problem of carcinoma of the Bartholin gland in 1953 as the result of a case that we had on the Gynecological Tumor Service at the State University of New York. Dr. Sidney Goss and I made a survey of the literature. We found that there had been some 116 cases reported up to that time.

In conjunction with some of the comments that have been made by the previous discussants, I think that our survey, as published in 1955, would indicate that the extension of radical surgery to the disease has been associated with an improvement in the end results that parallels the extension of radical surgery to the more common varieties of carcinoma of the vulva.

There are some further pertinent comments that might be made on the basis of our survey. The reported cases indicate that this is a disease found in younger age groups than is the usual carcinoma of the vulva. The latter is most frequently seen in the seventh and eighth decades. The peak incidence in our analysis was actually around the fifth decade. This fact might implicate inflammation as a predisposing factor.

Although we commonly consider Bartholin gland carcinoma to be of an adenomatous variety, a review of the literature shows that half of them are epidermoid and half of them are adenomatous. Some work in this connection by the German investigators, Sitzenfrey and Schweizer, indicates that inflammation may produce a metaplasia in the Bartholin gland. Hence, infection may possibly be a predisposing factor in the appreciably increased incidence of epidermoid carcinoma. Since, however, the ducts of the Bartholin gland are lined by epidermoid cells, they could very well be the site of origin of many tumors.

In conclusion, I certainly agree with Dr. Smith and Dr. Twombly that radical surgery appears to be the best treatment that one can offer these patients, and that, with the extension of this procedure to Bartholin gland carcinoma, one should anticipate a survival rate comparable to that seen in other types of carcinoma of the vulva.

## PAGET'S DISEASE OF THE VULVA

### Report of a Case and Review

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SINCE Paget<sup>1</sup> first described the mammary lesion which bears his name, and which presents a characteristic picture both clinically and histopathologically, the nature of the typical clear hydropic cell found in Paget's disease has been the subject of vigorous discussion and debate. As various theories and viewpoints have been advanced, it has become clear, as pointed out by Pinkus and Gould,<sup>2</sup> that these theories could be readily summarized. According to these authors, then, the Paget cell may be regarded as either: (1) an autochthonous, altered epidermal cell, changed regressively, i.e., degenerated and dyskeratotic, or changed progressively, i.e., dedifferentiated and anaplastic; or (2) a cancer cell representing an intraepidermal metastasis from a malignant tumor originating in the mammary gland or its ducts.

As clinical and pathological experience was accumulated, it soon became evident that Paget's disease occurred rarely in sites other than in the mammary areola, presenting a histopathological picture identical with that seen in the breast. So arose the concept of extramammary Paget's disease. According to Pinkus and Gould extramammary Paget's disease is an instance of one of the following: (1) Bowen's dermatosis, (2) erythroplasia of Queyrat, (3) superficial epidermoid carcinoma, (4) nevocarcinoma, (5) sweat gland carcinoma, or (6) carcinoma of the mucous membranes bordering on the skin.

Bowen's dermatosis presents in general a quite different picture, and the same may be said for superficial epidermoid carcinoma. Erythroplasia of Queyrat<sup>3</sup> is said to be the counterpart of Bowen's disease on mucous membranes, usually occurring on the glans penis, occasionally on the prepuce, vulva, or oral mucosa.

Pinkus and Gould stressed that Paget's disease, both mammary and extramammary, is an expression of a more or less well-balanced symbiosis of the epidermis and an epidermotrophic strain of cancer cells of more or less remote origin. This symbiosis they called the Paget phenomenon. The authors concluded, then, that extramammary Paget's disease is the result of the intraepidermal spread of either carcinoma of the apocrine sweat glands, carcinoma of the mucous membranes bordering on the skin, or amelanotic melanoblastoma with marked intraepithelial spread.

Stout,<sup>4</sup> in a very interesting paper, pointed out that extramammary Paget's disease does occur, usually secondary to carcinoma of the apocrine glands. These glands are found in the axilla and anogenital regions. Other cases of extramammary Paget's disease, he stated, can be finally classified as

either superficial basal-cell carcinomas, Bowen's disease, or squamous-cell carcinoma. A handful of cases remain, clinically and histopathologically indubitably Paget's disease, which have occurred on parts of the body where there are no apocrine glands. The author abstracted 6 cases, occurring on the forearm, scapula, axilla, buttock, below the left knee, and on the right eyebrow. Stout's own case presented in the left popliteal space, and showed the typical changes of Paget's disease. He believed these cases to be instances of amelanotic melanoblastoma with intraepithelial spread. Should such lesions occur in the anogenital region, or in the axilla, it would be impossible to differentiate them from apocrine gland carcinoma showing the Paget phenomenon.

The Paget phenomenon is also illustrated by a case of Ortega, Whitmore, and Murphy.<sup>5</sup> Their case was a widespread in situ prostatic carcinoma with intraepithelial extension into the urethra and urinary bladder, producing a picture histologically identical with Paget's disease.

An unusual combination in the production of extramammary Paget's disease has been recorded by Eversole.<sup>6</sup> In his case the neoplastic cells were found growing in the otherwise normal epithelium of the abdominal wall. The tumor cells apparently arose from a cutaneous implant of a papillary epidermoid carcinoma of the urinary bladder.

Dockerty and Pratt<sup>7</sup> presented the cases of 2 male patients aged 46 and 72, in whom, as a complication of Grade IV adenocarcinoma of the rectum, perianal Paget's disease was observed. The so-called Paget's cells were atypical and were "signet ring" in form. The authors feel that these observations reinforce the concept of the essentially metastatic nature of the Paget cell.

Aside from these interesting observations, however, most observers feel that the vast majority of cases of extramammary Paget's disease arise as the intraepithelial spread of underlying apocrine sweat gland carcinomas. This theory is borne out by the fact that these lesions occur almost exclusively in the axilla and anogenital regions, or in precisely those areas where apocrine sweat glands abound. However, in about only one half of the recorded cases has it been possible to demonstrate underlying sweat gland malignancy, although with study by serial sections it might have been demonstrated in all.

With these concepts in mind, we wish to report another case of extramammary Paget's disease of the vulva.

E. H., aged 70, a housewife, was admitted to the Roger Williams General Hospital on Aug. 22, 1956. She complained of vaginal bleeding and vulvar itching. The patient had had three normal pregnancies and an uneventful menopause at the age of 46 years.

For four years the patient had suffered from itching of the left labium. The itching had never subsided, but rather had increased in intensity, and the left labium had become moist and excoriated. Two years before the patient had bled vaginally for one day. This bleeding did not recur until about three weeks prior to admission, but since that time there had been daily spotting.

Physical examination showed the left labia to be excoriated, red, thickened, and weeping. A small polyp protruded from the external cervical os. The remainder of the physical examination was negative.

The operation consisted of a subtotal extirpation of the left labium, cauterization of the cervix, and removal of the cervical polyp.

The pathological specimen was an elliptical piece of tissue measuring 5.2 by 1.5 by 0.4 cm. The skin surface was yellowish to bluish gray, and was mottled, presenting several areas which were scaly and brownish yellowish gray in color. These areas were thickened and indurated. The subcutaneous tissue was uniformly yellowish grayish pink in color and had the appearance of areolar tissue.

Microscopically, the labium exhibited hyperkeratosis and parakeratosis, and in some areas there was a marked thickening of the stratum granulosum. There was a marked acanthosis with blunting and elongation of the rete pegs. The basal and Malpighian layers of the epidermis were invaded by groups and sheets of large, clear, hydropic cells (Fig. 1). These cells possessed an abundant clear or foamy cytoplasm with rather ovoid nuclei (Fig. 2). The nuclei varied somewhat in size, shape, and staining. Mitoses were fairly common. The nucleoli tended to be prominent.

Fig. 1.

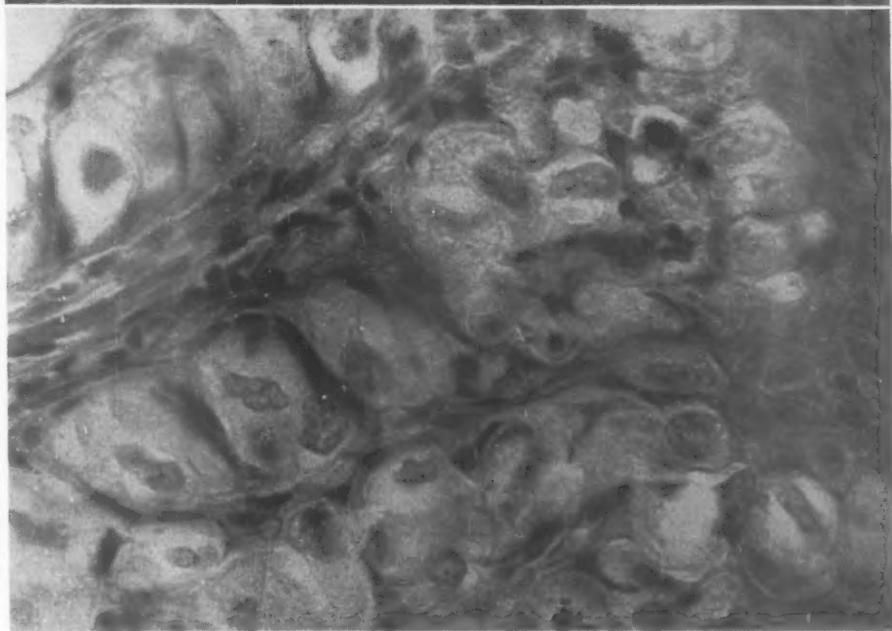


Fig. 2.

Fig. 1.—The epidermis is invaded by sheets of Paget cells. A hair shaft is invested with a rim of these cells.

Fig. 2.—The foamy cytoplasm and nuclear variations are apparent in these Paget cells.

In many areas these cells had destroyed or obscured the normal architecture of the epidermis. A few isolated Paget cells had penetrated as far as the stratum granulosum (Fig. 3). In the upper corium there was a well-demarcated zone of nonspecific chronic inflammation.

Fig. 3.

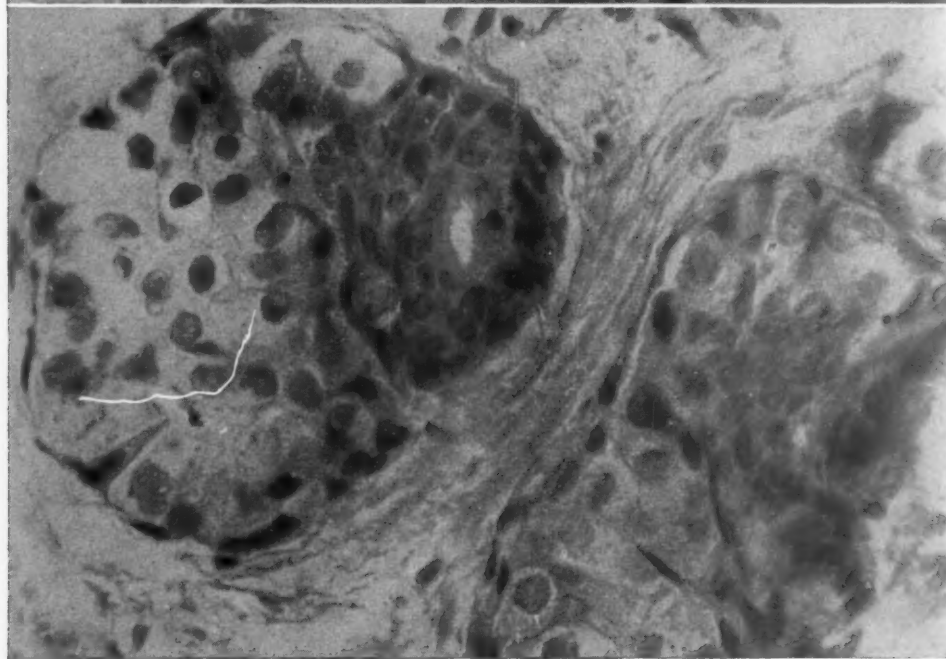
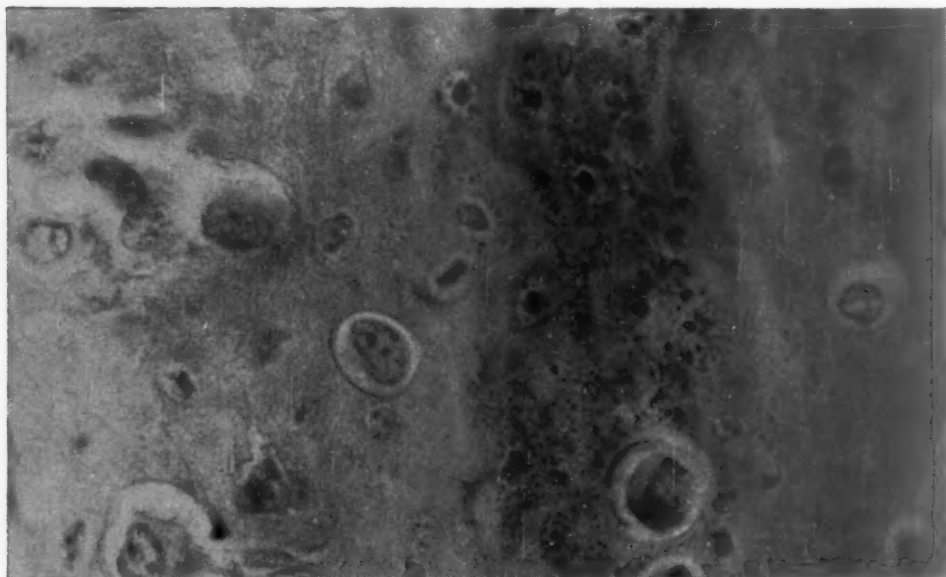


Fig. 4.

Fig. 3.—Isolated Paget cells have penetrated into the stratum granulosum.

Fig. 4.—Proliferation of Paget cells in sweat glands.

Evidence of sweat gland participation was sought for carefully, throughout many sections, during which the entire gross specimen was sacrificed for histopathological study.



One field was found in which sweat gland participation in this malignant process could be demonstrated (Fig. 4).

*Pathological Diagnosis.*—Extramammary Paget's disease of the vulva, with underlying sweat gland carcinoma.

Postoperatively a total of 2,100 r was administered to the area of operation. A follow-up after five months shows complete healing and to date there is no evidence of recurrence.

### Comment

Weiner<sup>8</sup> in 1937 reviewed the subject of extramammary Paget's disease, collecting 7 well-authenticated cases of vulvar Paget's disease and adding one of his own. After his review and that of Pinkus and Gould,<sup>2</sup> only sporadic reports of vulvar Paget's disease have appeared in the literature.

Milroy<sup>9</sup> in 1946 presented a case of Paget's disease of the vulva in a 74-year-old white woman, but was unable to demonstrate underlying sweat gland carcinoma.

Casper<sup>10</sup> in 1948 reported a case of vulvar Paget's disease in a 66-year-old patient. No underlying sweat gland carcinoma was demonstrated, and the author felt that the entire lesion, in these cases, should, if possible, be studied by serial section. This author claimed that his was the ninth reported case of this disease.

Another case was reported by Sonck,<sup>11</sup> occurring in a 61-year-old woman. In his case pagetoid proliferation of cells could be seen in the underlying sweat glands.

Huber, Gardiner, and Michael<sup>12</sup> presented 3 more cases in patients aged 64, 74, and 68. In all these women, the disease had been present many years; in one for 17 years.

The authors stated that, including their 3 cases, 15 cases of vulvar Paget's disease had been reported.

Vermenouze<sup>13</sup> presented still another case of vulvar Paget's disease, in a 56-year-old woman. His article made no reference to an underlying sweat gland malignancy.

Dockerty and Pratt<sup>7</sup> recorded 2 additional cases of Paget's disease of the vulva. Both were atypical in that the cells assumed predominately a "signet ring" morphology. In the first woman, aged 56, there was an underlying adenocarcinoma in the corium, Grade IV. In their other patient, aged 58, the lesion was first regarded as a Grade II epithelioma in situ of the epidermis, but upon review it was regarded as extramammary Paget's disease. The cells were, for the most part, of the "signet ring" type and the underlying apocrine sweat glands were affected.

Paget and his co-workers<sup>14</sup> described still another case of Paget's disease of the vulva in a white woman 79 years of age. An underlying sweat gland carcinoma was not mentioned.

Another case was recorded by Naylor<sup>15</sup> in a 66-year-old woman. No sweat gland carcinoma was detected. Federici<sup>16</sup> added still another case to the literature.

Woodruff<sup>17</sup> published 2 more cases, one in a woman 50 years old, and the other in a woman 60 years of age. In the second, but not in the first case, was there evidence of sweat gland involvement.

A very unusual instance of vulvar Paget's disease was published by Plachta and Speer.<sup>18</sup> Their patient, 64 years of age, showed at autopsy an adenocarcinoma of the vulva arising in the apocrine glands, with metastases

to the heart, lungs, spleen, liver, adrenals, kidneys, sacral, lumbar, and dorsal vertebrae, lymph nodes, and bone marrow. In the vulva the picture was that of extramammary Paget's disease. The metastases presented the pattern of an adenocarcinoma with large clear cells.

Bowman and Hartman<sup>19</sup> studied a case of vulvar Paget's disease in a white woman 42 years of age. The patient was alive twelve years after vulvectomy, but they were unable to demonstrate any sweat gland carcinoma. The authors stated that in only about one half of the reported cases is it possible to find such an underlying sweat gland carcinoma. They estimated the total number of reported cases of this disease, including their own, as 17.

Herzberg<sup>20</sup> recorded a case of Paget's disease of the vulva without demonstrable sweat gland carcinoma, and Eisenberg and Theuerkauf<sup>21</sup> presented another with an underlying adenocarcinoma in the corium. Both patients were 51 years of age.

Finally, Haines<sup>22</sup> added to the literature another case of Paget's disease of the vulva without demonstrable sweat gland carcinoma, found in a white woman 51 years old.

### Summary

1. A case of extramammary Paget's disease of the vulva is described in a 70-year-old white patient with pagetoid proliferation in the underlying sweat glands. This is believed to be approximately the twenty-eighth case of vulvar Paget's disease recorded in the literature.

2. Various theories as to the mechanism and modus operandi of the Paget phenomenon, both mammary and extramammary, are discussed and reviewed.

3. Other published cases of vulvar Paget's disease are reviewed.

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## METHOTREXATE THERAPY OF METASTATIC CHORIOCARCINOMA

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CHORIOCARCINOMA arising in the products of conception is a highly malignant tumor. Death usually follows shortly upon the appearance of disseminated metastatic disease. Although spontaneous remissions have been reported, and often cited, they do not occur with regularity. Further, it is not certain how many patients with remissions really had chorioadenoma destruens, a neoplastic disease with more favorable outlook. Choriocarcinoma is commonly refractory to x-irradiation. Remissions in disseminated choriocarcinoma after the use of testosterone propionate,<sup>1</sup> mechlorethamine (nitrogen mustard),<sup>2</sup> and urethane<sup>3</sup> have been reported, although the data, follow-up, and isolated experiences do not allow appraisal of the therapeutic effect of these drugs.

Recently, Li, Hertz, and Spencer<sup>4</sup> reported the use of Methotrexate\* (Amethopterin) in 2 patients for choriocarcinoma with pulmonary metastases. A third patient with chorioadenoma destruens was treated in similar fashion. Remarkable improvement was noted in each patient. Substantially elevated titers of urinary chorionic gonadotrophin were reduced progressively to levels near vanishing. Metastatic nodules in the lungs diminished greatly.

The method of administration of Methotrexate to Li's patients was unconventional, when judged by ordinary doses of this folic acid antagonist for patients with acute leukemia. Studies of Goldin<sup>5</sup> measuring the therapeutic effect in mouse leukemia, and of Condit<sup>6</sup> measuring conversion of folic acid to folinic acid in man afford experimental basis for interrupted large-dose folic acid antagonist treatment. In Li's patients, initial intravenous loading doses of Methotrexate were followed by repetitive oral courses of 3 to 5 days' duration at a dosage of 25 mg. daily. The daily oral dose was thus 5 to 10 times the average adult dose used in acute leukemia, and the treatment was administered in an interrupted fashion.

The subject of this case report is a woman with choriocarcinoma treated by a method similar to that Li has reported. The very favorable response in this case, the third successive choriocarcinoma to be benefited by the regimen, after Li's 2 cases, supports the interpretation that a true drug effect has been observed. Since this patient was treated, Li has observed another woman with choriocarcinoma who responded favorably.<sup>7</sup>

\*Methotrexate is the trade name for 4-amino-N-10-methyl-pteroylglutamic acid and is manufactured by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

## Case Report

S. S. is a 33-year-old white married woman who was referred to the Roswell Park Memorial Institute for choriocarcinomatous metastases to the lungs.

Her first pregnancy in 1953 resulted in a stillborn infant at 7 months. A normal girl was born in 1954. On Sept. 11, 1956, a normal boy was delivered. During the course of this third pregnancy she noted intermittent vaginal bleeding, and in the postpartum period repeated vaginal hemorrhages. Abdominal pain appeared. Three liters of blood were given for continuing severe hemorrhage. A curettage was performed and the curettings were interpreted as choriocarcinoma. A total hysterectomy with salpingo-oophorectomy was performed 45 days after delivery on Oct. 26, 1956. A submucosal tumor 3 cm. in diameter infiltrating the posterior uterine wall was present. Interpretation of slides from this specimen confirmed the diagnosis of choriocarcinoma. No villi were seen. This material has been reviewed and the diagnosis substantiated by the Armed Forces Institute of Pathology.

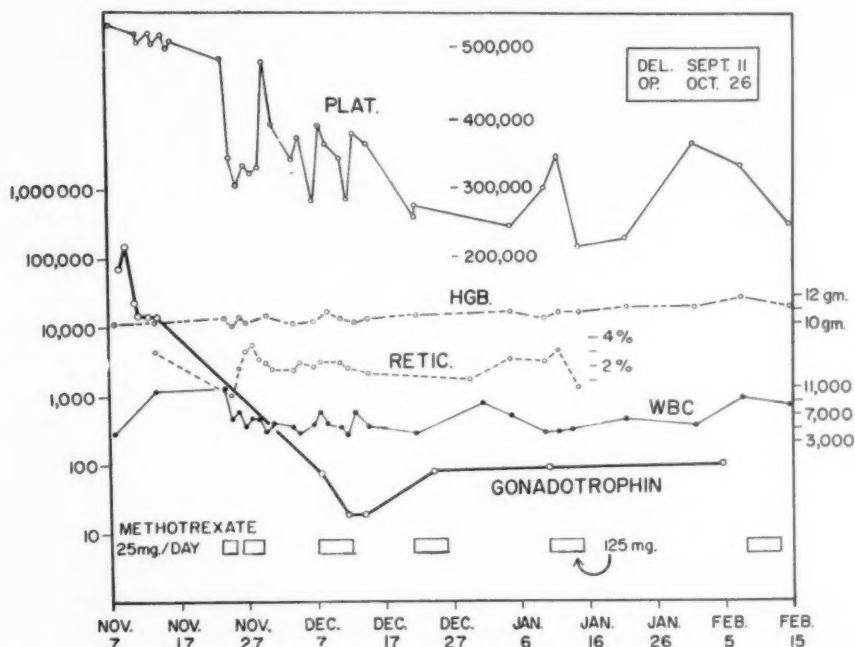


Fig. 1.—Changes in hematological values and urinary gonadotrophin during treatment with high-dose interrupted Methotrexate. Arithmetic scales for platelets and reticulocytes are in center, for hemoglobin and white blood cells at right. Semilogarithmic scale for gonadotrophin plotted on left.

A chest x-ray disclosed multiple lesions characteristic of hematogenous metastases. At this time she was transferred to the Medicine A Service, Roswell Park Memorial Institute. On admission, on Nov. 7, 1956, no information of importance other than the present illness was elicited. She did not cough; there was no pain; she was ambulatory in so far as her postoperative condition permitted; her weight was constant at 75 kilograms (165 pounds). Physical examination disclosed no abnormalities except for a healing hysterectomy scar and a pelvic mass.\* At the apex of the vaginal vault on the left side a mass was felt which measured 5 to 6 cm. in diameter. It was not certain whether this mass was a postoperative hematoma or recrudescant tumor. Urinalysis disclosed bacteriuria, pyuria, and proteinuria. A urine culture showed innumerable colonies of *E. coli*. The abnormal urine findings disappeared without specific antibacterial treatment.

\*I am indebted to Dr. Raymond Mitchell, who brought this patient to my attention, and who rendered gynecological consultation.

The hemoglobin concentrations, white blood cell, platelet, and reticulocyte counts are shown in Fig. 1. The levels of chorionic gonadotrophin\* in the pretreatment period fell from a titer in excess of 100,000 to a plateau at more than 10,000 but less than 25,000 M.U. Progressive increase in the size of pulmonary lesions before treatment is seen in Figs. 2 and 3.



Fig. 2.

Fig. 2.—Nov. 7, 1956. On admission.



Fig. 3.

Fig. 3.—Nov. 23, 1956. Beginning of treatment.

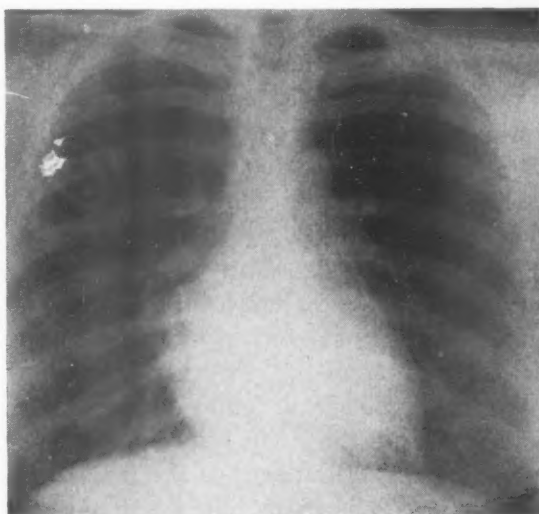


Fig. 4.

Fig. 4.—Jan. 10, 1957. After third course of Methotrexate.



Fig. 5.

Fig. 5.—May 9, 1957. After sixth course of Methotrexate.

Methotrexate administration was begun at 25 mg. given once per day. After the second day a small vesicle was seen on the tongue, but this was evanescent and atypical. The

\*The gonadotrophin titers were performed in the laboratories of Dr. Roy Hertz.



drug was restarted on the following day. The first course of Methotrexate therefore was 125 mg. in 6 days, whereas all subsequent courses were 125 mg. in 5 days.

During the course of administration, progressive diminution in the pulmonary lesions was noted (Figs. 4 and 5). The mass detected on pelvic examination became smaller and, on Feb. 15, 1957, was no longer identifiable. A chorionic gonadotrophin titer obtained after the first course of the drug showed a fall from her pretreatment level to less than 100 M.U., a normal value in the oophorectomized woman. Subsequent titers have all been normal.

Accompanying the administration of Methotrexate was evidence of drug effect on the patient distinct from the effects on her tumor. A progressive fall in platelet count was noted. On two occasions the reticulocyte count dropped below 1 per cent, but at other times was well maintained. No important change in hemoglobin or leukocyte concentrations was seen.

After each course of drug administration other evidence of toxicity was apparent. Starting with the first course, ulceration of the buccal, lingual, and pharyngeal mucosa appeared (excluding the equivocal lesion during the first course) as early as one day after a course of administration, and new lesions appeared as late as 17 days. Abdominal cramps, frequent defecation, and diarrhea began during the last days of treatment courses and persisted 3 to 6 days, starting with the second course. Folliculitis around the hair roots at the nape of the neck appeared at the end of the treatment courses, beginning with the third course. Anal pruritus and dermatitis of the auditory canal were seen on isolated occasions after administration of the drug. The toxic lesions in the mouth were more severe, continued to appear for several more days, and persisted longer after the later courses. No toxic effect on the liver or kidneys was noted.

The patient remains in remarkably good health (September 15, 1957). There is no evidence of tumor in lungs or pelvis. We plan to administer Methotrexate repeatedly at intervals of 30 to 60 days, dependent on evidence of toxicity, in an attempt to continue the suppression of the tumor, if any remains.

### Comment

The administration of Methotrexate in this patient was associated with unequivocal remission of metastases from choriocarcinoma. A return to normal in urinary chorionic gonadotrophin titers was also seen. Li and his collaborators<sup>4, 7</sup> have reported 3 cases of choriocarcinoma and one of chorioadenoma destruens which responded equally dramatically. The fact that this patient is one of 4 who had choriocarcinoma, similarly treated, who have had remissions after Methotrexate administration, fortifies the impression that the responses have not occurred by chance.

It seems highly likely that several patients with choriocarcinoma have been treated with folic acid antagonists according to conventional dose regimens, because the effects of these antimetabolites on the products of conception have been stressed. Such an experience has not been found in a brief survey of the literature, however, and it is probable that, had impressive remissions occurred, they would have been reported. Whether it is the large-dose intermittent Methotrexate treatment that caused the remission in our patient, whether it is a hitherto unrecognized propensity of this neoplasm, or whether *both* situations must obtain cannot at this time be stated.

It has not yet been established that the dosage regimen described by Li and used here is optimal. One can only declare pragmatically that it has worked repeatedly. In the absence of renal insufficiency, pre-existent hematopoietic depression, and cachexia, the doses described may be given cautiously

under daily supervision. For this patient, toxicity has been moderately severe but not life threatening. In 2 of 8 other patients with metastatic carcinoma from various other sites treated in similar fashion, however, profound toxicity evidenced by pancytopenia and ulceration of the alimentary canal was present at the time of death.<sup>8</sup> Further experience and cautious trial will be required before the best method of Methotrexate administration is established.

### Summary

A patient with choriocarcinoma extensively metastatic to the lungs (and probably pelvis), with elevated urinary gonadotropin titers, has been treated with Methotrexate. The drug was administered orally in intermittent high-dose courses. Regression of tumor masses and fall of gonadotrophin excretion followed. This experience confirms that reported by Li, Hertz, and Spencer.<sup>4</sup>

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## Case Reports

### CANDIDA ALBICANS INFECTION OF THE AMNIOTIC SAC

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**T**HIS is a report of what is believed to be the first recorded instance of *Candida albicans* infection of the umbilical cord.

The mother of this conceptus was a 36-year-old gravida ii, para i, white woman, who had had one cesarean section in 1955 because of cephalopelvic disproportion. In 1953 she had had a curettage for endometrial hyperplasia. The present pregnancy began in January, 1956, and the expected date of confinement was Oct. 9, 1956.

When the patient first presented herself to her obstetrician on March 1, 1956, she stated that she had experienced a burning sensation in the vagina for which she had been using Floraquin\* tablets. Following this treatment symptoms improved. In the past she had had a trichomonal vaginitis. Fungi had never been isolated. She was said to be sensitive to penicillin.

On June 24, 1956, in the sixth month of pregnancy, the patient went into labor. She bled moderately during labor and a transfusion of 500 c.c. of whole blood was necessary before delivery. Approximately 19 hours after the onset of labor a female anencephalic fetus was delivered as a breech. The fetus weighed 630 grams and died within 40 minutes. No autopsy was performed.

The exact time of rupture of the membranes is not known. The patient was not aware of their having ruptured prior to labor, however, and, for this reason, it is assumed that rupture occurred within the 19 hours preceding delivery.

The placenta (No. CS56-72) was examined and blood sampled for reasons not pertaining to the present problem. The placenta weighed 430 grams, the edematous cord was 23 cm. in length and was inserted eccentrically. The membrane appeared complete and rupture had occurred 6 cm. from the margin. The fetal surface was dull, yellowish, and opaque. The umbilical cord was slightly brownish in color. Section of the placental tissue disclosed no unusual findings.

\*G. D. Searle & Co., Chicago, Ill.

The tissue was fixed in Bouin's fluid and cultures were taken from the surface of the umbilical cord and the fetal surface of the placenta. Routine hematoxylin-eosin slides were prepared from paraffin blocks and some sections were stained with the periodic acid-Schiff method. Examination of these slides showed normal immature placental tissue without evidence of inflammation or degeneration. The fetal surface, however, showed a severe degree of chorioamnionitis in all sections examined from various locations in the placenta. The amniotic epithelium was almost completely degenerated. The underlying connective tissue of amnion and chorion was markedly infiltrated by acute inflammatory cells. These polymorphonuclear leukocytes (maternal) formed a dense layer on the surface of the placenta and were enmeshed in fibrin; many were in the process of degeneration (Fig. 1). The reaction extended into the walls of the large surface fetal vessels. Sec-

Fig. 1.

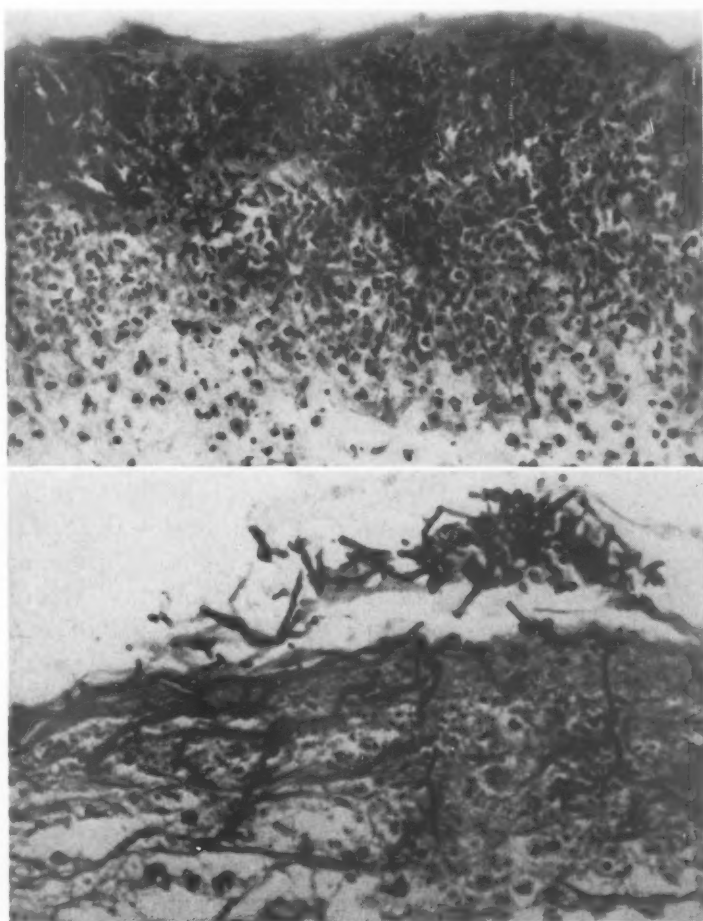


Fig. 2.

Fig. 1.—(BLIH CS56-72.) Fetal surface of placenta. Dense infiltration with polymorphonuclear leukocytes, fibrin deposition, and fibroblastic reaction in chorion. Amniotic epithelium is destroyed. (Hematoxylin and eosin.  $\times 300$ ; reduced  $\frac{1}{4}$ .)

Fig. 2.—(BLIH CS56-72.) Surface of umbilical cord (mid-portion). Note: Surface fungus growth and invasion of cord substance by *Candida*. Scattered inflammatory-cell response. (PAS stain.  $\times 350$ ; reduced  $\frac{1}{4}$ .)

tions of the umbilical cord showed acute inflammatory cells (fetal) in the walls of the umbilical vessels as well as the cord substance. More remarkable, however, was the finding of large fungus colonies (Fig. 2) on the surface of the umbilical cord. These organisms were seen to invade the cord substance superficially and a focal inflammatory-cell

infiltrate had resulted in these regions. The fungi were surrounded by debris and some fibrin and stained a deep purple with the PAS stain. No such organisms were seen in the granulation tissue-like inflammation on the surface of the placenta. No bacteria were identified histologically nor were they present by culture.

Scrapings of the surface of the umbilical cord and amnion grew pure cultures of *Candida albicans*.\*

### Comment

*Candida albicans* infection of the vagina during pregnancy is a frequent complication. It is asymptomatic in approximately 50 per cent of the cases.<sup>1</sup> Jackson<sup>1</sup> studied 668 consecutive obstetric patients and found an incidence of 33.6 per cent in pregnant Filipino patients. Occasionally, the fungus was associated with *Trichomonas vaginalis*. While the disease commonly has no ill effect on the course of pregnancy or development of the infant, occasionally the monilial vaginitis has been implicated as the source of fungi causing thrush in a newborn infant. Transplacental infection with fungi or ascending infection has not been recorded in the literature to the best of our knowledge.

The problem of chorioamnionitis and its association with intrauterine pneumonia is an old one. Perhaps the most careful and extensive study of this subject is that by Wohlwill and Bock.<sup>3</sup> More recently, however, a number of authors<sup>4-6</sup> have concerned themselves with this problem. While it is fairly generally agreed now that the fetus may become infected by inhaling infected amniotic fluid, the modus operandi of the primary infection is not entirely clear. It appears that in most instances the ascending infection of the membranes either leads to or follows premature rupture of the membranes.<sup>6</sup> Nevertheless, a certain number of cases remain in the files of all careful observers in which no history of premature rupture of the fetal membranes can be obtained, yet the membranes may be severely inflamed. There may be extensive funiculitis (indicating fetal response to infection) and often the fetus will show abnormal behavior in the first few days of life.

The case under discussion falls into this latter group. There was no history of rupture of the membranes and despite a labor of only 19 hours an extensive chorioamnionitis, fetal "vasculitis," and surface funiculitis may be seen. Inasmuch as there is no evidence of placental villus inflammation and since the patient's history suggests the presence of antecedent moniliasis, it seems probable that this patient had a subclinical rupture of the membranes with infection and subsequent sealing of the site of rupture. If this is the only possible explanation in the present case, we feel that this entity merits further attention in the exploration of the considerable number of "congenital pneumonias."

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\*Courtesy of Dr. G. E. Foley, Children's Medical Center, Boston, Mass.



## BILATERAL THECA LUTEIN CYSTS OF THE OVARY IN A CASE OF ERYTHROBLASTOSIS

### Presentation of a Case

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THE high incidence of bilateral symmetrical lutein cysts of the ovary in cases of hydatidiform mole and chorionepithelioma is common knowledge. Outside of these two conditions, multiple follicle cysts have been observed in Cushing's syndrome, growing to the size of a fist, rarely larger. A few instances of these cysts have been described associated with disease of the anterior pituitary gland as in basophile adenoma, and also with functional psychoses.<sup>1</sup>

In pregnancy not associated with hydatidiform mole or chorionepithelioma, the presence of these lutein cysts appears to be very rare, only 2 cases having so far been reported. In 1942 Schultheiss-Linder<sup>2</sup> reported a case of bilateral theca lutein cysts associated with nephropathia of the mother and hydrops fetalis. She cited another case of bilateral lutein cysts in the presence of fetal hydrops reported by Bürger.<sup>3</sup>

We are reporting a case of bilateral theca lutein cysts in a pregnancy with erythroblastosis of the fetus.

Mrs. A. M., a 27-year-old white woman, was admitted on Dec. 8, 1954, at 12:15 A.M., apparently in labor, with fairly strong, regular, abdominal pains, every six minutes, lasting for 30 seconds. The expected date of confinement was Jan. 23, 1955.

Her first child was delivered by cesarean section at 8 months' gestation because of placenta previa in 1949. A normal, live baby boy weighing 5 pounds, 3 ounces was delivered. The patient is Rh negative. Her second pregnancy terminated in abortion in 1952 at 10 weeks' gestation. During the present pregnancy she had been receiving weekly injections of progesterone.

Examination on admission showed the height of the fundus to be approximately 4 fingerbreadths above the navel. Fetal heartbeats could not be distinctly heard. The patient claimed that she had not felt any fetal movements for about 4 weeks, but the day before she was admitted the fetal heartbeats were heard at the doctor's office. Pelvic examination showed a rather thick, soft cervix with 1 cm. dilatation of the external os.

Urinalysis, blood, and differential count were essentially normal. Rh studies showed incomplete antibodies present in a dilution of 1:256. She was negative for the "D" factor, positive for the "C" factor. Anti D antibodies were present in high titer. Her husband was D<sub>C</sub> positive (heterozygous).

The patient was taken to the operating room for cesarean section. Upon opening of the abdominal cavity, the main finding was that of an enlarged pregnant uterus with bilateral, grapefruit-sized, reddish and dark brown polycystic ovaries. A stillborn baby

boy that weighed 5 pounds, 6 ounces, was delivered by cesarean section at 1:45 A.M. The section was followed by subtotal hysterectomy and bilateral salpingo-oophorectomy. Postoperatively the patient had an uneventful course.

**Surgical Specimens.**—Attached to the uterus were both ovaries which were transformed into large cystic masses, measuring approximately 13 by 10 by 6 cm. each. On opening, numerous thin-walled cysts with watery content were seen, some of them filled with coagulated blood, and ranging in size up to 5 cm. in diameter.



Fig. 1.—Gross specimen.

**Microscopic Findings.**—In one area of the uterus there was a remnant of placenta, in which the villi showed relatively dense interstitial fibrosis and preservation of the Langhans' layer. There was nowhere evidence of chorionepithelioma or hydatidiform mole. The ovarian cysts showed very marked theca-cell luteinization. Occasionally there was a cyst in which the slightly swollen granulosa cells were preserved, but in most of them the granulosa was inconspicuous, flattened and separated from the greatly swollen eosinophilic theca cells by a layer of loose fibrous tissue. A few cysts showed marked luteinization of both the granulosa and the theca cells. Some of the cysts showed hemorrhages, probably due to the excessive congestion in the vascular system in their walls. There was marked interstitial edema.

Fluid from the several ovarian cysts was aspirated and injected in rabbits for pregnancy tests, which proved strongly positive.

Postmortem examination of the fetus showed a stillborn male baby weighing 5 pounds, 6 ounces. The skin showed beginning maceration; large pieces of skin could be pulled off from the baby. The abdomen was distended, but soft. No jaundice was noted.

**Diagnosis.**—Findings compatible with fetal erythroblastosis. The microscopic findings showed an advanced degree of postmortem autolysis.

#### Process of Formation of Theca Lutein Cysts

The main physiologic characteristic in the formation of the luteinized cysts in hydatidiform mole and chorionepithelioma is apparently the enormously increased production of chorionic gonadotropic hormone. According to Seitz<sup>4</sup> and Wallard (as quoted by Schultheiss-Linder), these cysts have their origin in atretic follicles in which the connective tissue cells of the theca interna are changed into theca lutein cells. Schroeder, also quoted by

Schultheiss-Linder, thinks that these cells originate from granulosa cells and he tried to demonstrate that fact through the different stages of follicle formation. In our case, the process is one of exaggerated luteinization affecting

Fig. 2.

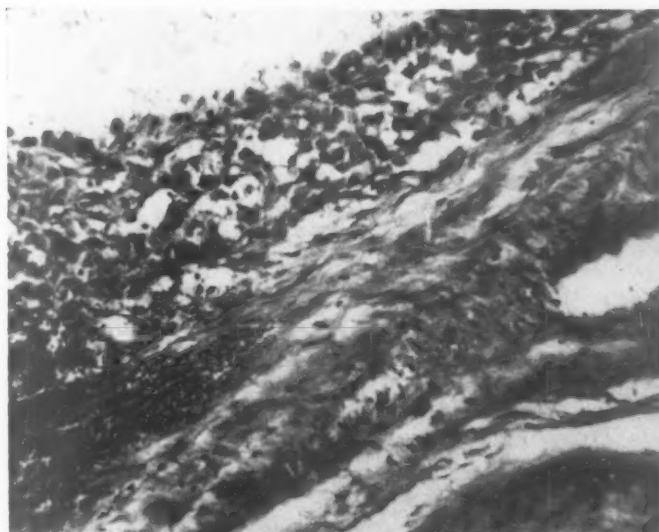


Fig. 3.

Fig. 2.—Wall of a granulosa lutein cyst.

Fig. 3.—Wall of theca lutein cyst (arrow) showing two layers of luteinized theca cells.

chiefly the theca lutein cells, the granulosa layer also taking part, but to a much lesser degree. In all cases reported in the literature, the cysts are multiple, attaining considerable size, sometimes up to that of an orange or even bigger, and they are filled with clear or slightly turbid fluid. Experimentally, small cysts of the ovary of similar structure can be observed after injection or implantation into animals of hormones of the anterior pituitary gland or after injection of extract of the placenta or urine of pregnant women. Zondek and Heyman<sup>5</sup> discovered that giving massive doses of prolactin to patients suffering from carcinoma of the cervix produced corpus luteum

hematomas, their results paralleling those of animal experiments. A comparable cystic condition in the ovarian follicles can be produced in the human by parenteral administration of commercial gonadotropic hormone.

Schultheiss pointed to the fact that atresia of follicles with luteinization is not specific for hydatidiform mole and chorionepithelioma but may also occur to a lesser degree in normal pregnancy. These luteinized follicles may be seen in two forms, sometimes as collapsed and atretic cysts, retaining the outline of a corpus luteum, and also as round cysts of varying, mostly small, sizes. There is a great difference, however, between the cysts of normal pregnancy and the large cysts in hydatidiform mole, and in the 3 cases with which this paper deals these were evidently the product of stormy chorionic gonadotropic hormone production.

The case here presented is one of erythroblastosis fetalis due to Rh incompatibility; in the year 1942, at the time of Schultheiss and Burger's publications, the connection of fetal hydrops with erythroblastosis fetalis and Rh incompatibility was not generally known, but we can with great probability assume that the cases of both were of this type. It seems quite possible that these cysts occur in erythroblastosis much more commonly than we know, because the coincidence of delivery by cesarean section and fetal erythroblastosis, with, therefore, the opportunity to examine the ovaries in cases of erythroblastosis, is rare. This may account for the fact that we were unable to find other cases in the literature.

We should like to point to an anatomic factor present in both erythroblastosis and hydatidiform mole which may have some bearing upon the origin of these cysts. This common factor is the preservation of the Langhans cell layer (cytotrophoblast) in both the hydatidiform mole and the erythroblastotic placenta. As is well known, the pregnancy tests weaken and finally become negative with the progress of a normal pregnancy. This occurs approximately simultaneously with the disappearance of the cytotrophoblastic layer in the placental villi. As a consequence, one feels tempted to postulate that the Langhans layer represents the site of placental gonadotropic hormone production. At this moment, no pertinent studies are known to us dealing with the persistence and quantitative evaluation of pregnancy tests in the last months of a pregnancy with erythroblastosis.

### Summary

The presence of large bilateral theca lutein cysts in pregnancy not associated with hydatidiform mole is apparently very rare, only 2 cases having been previously reported in the medical literature. A case of our own occurring at the Deaconess Hospital in Buffalo is added. In 2 of these 3 cases, fetal hydrops (before the Rh era) was reported; in our case fetal hydrops together with proved erythroblastosis due to Rh incompatibility was present. A theory is proposed correlating the anatomic findings in hydatidiform moles and in cases of erythroblastosis (persistence of the cytotrophoblastic layer which may be the site of gonadotropic hormone production).

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## PREGNANCY COMPLICATED BY SPONTANEOUS SUPRARENAL AND OVARIAN VENOUS HEMORRHAGE

### A Case Report

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THIS discussion concerns an instance of pregnancy complicated by unusual, spontaneous, catastrophic hemorrhage from the suprarenal and ovarian veins. The combination presented a problem in diagnosis and treatment.

An 18-year-old primigravida was hospitalized in the thirty-eighth week of pregnancy at 9:30 A.M., Sept. 30, 1956. The prenatal course had been uneventful until September 29. Then the patient experienced transitory, sharp pain in the right costovertebral angle. Since it disappeared quickly, she disregarded it. Approximately 24 hours later the excruciating pain reappeared suddenly as she sat down in a chair. Nearly two hours later, when hospitalized, the blood pressure was 110/90, the pulse 60 per minute, and the temperature 98.6° F. The skin was dry with good turgor. The mucous membranes were moderately pale. The head, neck, chest, heart, and lungs appeared essentially normal. The uterine fundus was soft, nontender, and within 4 cm. of the xiphoid process. The baby presented by the vertex. One observer thought the fetal heartbeat was faint for a short time. Light pressure over the right kidney posteriorly reproduced much discomfort. The cervix was long, uneffaced, and closed. Rectal examination added no information. There was no edema of the extremities.

The tentative diagnosis was renal colic with obstruction due to a stone, versus torsion or rupture of a viscus as a second choice.

#### *Hospital Course.—*

*Ante partum:* The patient did feel faint when placed in the erect position. This sign raised the question of internal bleeding or a neurogenic effect from pain. In anticipation of operative intervention a blood transfusion was started on the basis of a low hematocrit.

Symptoms and signs diminished during the next 3 hours. The blood pressure remained fairly stable and the pulse fluctuated between 70 and 80 per minute at different times. Undoubtedly the transfusion camouflaged the process of internal hemorrhage found later.

In the meantime 2 plus albuminuria and an abundance of white blood cells were found in a catheterized urine specimen. This observation supported the added diagnosis of acute pyelonephritis. On the other hand, it confused the interpretation of the situation at the time.

A hematocrit taken nearly 3 hours after the blood transfusion was started was only slightly higher than that obtained before the transfusion. The insignificant change indicated there was blood loss occurring. The uterus was still soft and nontender, while the pain had receded. Shortly thereafter retrograde pyelograms were made because of the original diagnosis and because severe, colicky pain recurred. The urinary tract proved to be normal. It was now 2:30 P.M. Five physicians experienced especially either in gynecic problems, urology, general surgery, or anesthesiology gathered to evaluate the situation. There was a difference of opinion as to the advisability of doing an exploratory procedure at this



time because localizing signs were nil and because the best route of exploration was in question. It was debatable whether the pathologic process was extraperitoneal and renal or intraperitoneal. The abdominal route was selected later when the right costovertebral pain recurred, epigastric discomfort appeared for the first time, the abdomen was equivocally "fuller" and the fetal heart rate dropped to near 100. Now the diagnosis entertained was concealed abruptio placentae associated with some other undetermined type of intra-abdominal pathology.

*Intra partum:* A low cervical cesarean section was done under epidural anesthesia. A very markedly enlarged right uteroovarian venous plexus was noted on first entering the abdomen. Free blood was present in the abdominal cavity. Initially this was suspected to have regurgitated from the oviducts. The uterus was bluer in color than normal. A concealed partial separation of the placenta occupied the right side of the uterine cavity. The amniotic fluid was clear, indicating that little, if any, blood had penetrated into the amniotic sac. Not until the baby and placenta were removed and the uterus was closed was it possible to see a large retroperitoneal hematoma in the right abdominal gutter. It extended from the right infundibulopelvic ligament to the diaphragm and medially beneath the first portion of the duodenum. As the hematoma was evacuated bloody ooze came from the ovarian plexus. This was excised. Still ooze continued to come from the region of the renal vessels. This bleeding ceased when a vein above the main right renal vessels was tied. Acute hypotension developed after the baby was extracted but the blood pressure returned to normal by the end of the operation. Up to this time 2,500 c.c. of blood had been given.

*Postoperatively:* Approximately one hour postoperatively the patient precipitously went into shock. The operative team theorized that bleeding was coming from elsewhere above the right kidney. An operative approach was made through an incision over the twelfth rib, which was removed. An estimated 500 to 800 c.c. of clotted blood was found extraperitoneally above the kidney. Bleeding came from multiple points surrounding the right adrenal gland and from the main venous channel leading from the suprarenal to the vena cava. It was necessary to remove most of the gland as well as to ligate the principal venous channel to the vena cava. Gelfoam and a pack were left in the pocket previously occupied by clot. Thirty-five hundred cubic centimeters of blood was given during this phase of treatment, bringing the total blood given to 6,000 c.c.

Two hundred milligrams of cortisone daily and 1 Gm. Combiotic every eight hours were given three and six days, respectively. The pack was removed by the third day. A temperature of 100 to 101° F., mild hypertension, and pulse over 100 persisted for the first 5 postoperative days. Thereafter each was within normal range. Eight months later the patient is well.

The final diagnoses included: concealed abruptio placentae, multiple hemorrhages from the suprarenal and ovarian venous plexuses, and pyelonephritis.

*Baby:* The baby weighed nearly 3,600 grams. It was born alive but died shortly after birth. Clinically the infant drowned from a waterlogged pulmonary system. Aspiration of the trachea by direct vision proved to be a futile procedure. Unfortunately, a postmortem examination was not granted but it is believed that the baby aspirated much amniotic fluid because of chronic intrauterine anoxia.

*Laboratory and roentgenographic studies:* The initial hematocrit was 30 vol. per cent with a red cell count of 3.09 million, a white cell count of 14,250, and a normal differential. The hematocrit taken 3 hours after the transfusion was started was 31 vol. per cent; the day after operation it was 39 per cent.

Albuminuria and pus were found before operation as previously mentioned. There were no microscopic elements or other abnormalities in the urine after the fifth postoperative day. The specific gravity ranged from 1.015 to 1.031 at various times.

Roentgenographic studies showed the normal physiologic dilatation of the ureters seen in pregnancy.

Tissues removed were histologically normal artery, veins, and adrenal gland.

### Comment

Keele and Keele<sup>5</sup> are quoted as being the first to differentiate between adrenal hemorrhage of the Waterhouse-Friderichsen syndrome and hemorrhage of a noninfectious variety. Others<sup>5, 6</sup> collected 36 instances of suprarenal hemorrhage of a noninfectious kind complicating pregnancy or the puerperium. Most of the hemorrhages occurred on the right side, in primigravidas, and nearly all died before a correct diagnosis was suspected. None survived. Usually the complication developed during the course of a pathologic gestation. The combination suggests more than a coincidental event.

Menaker and Cauble<sup>2</sup> collected 73 cases of rupture of the ovarian vessels in pregnant or puerperal patients. One half of them died. Some women required more than 10,000 c.c. of blood given as an emergency measure for survival. Hodgkinson's<sup>1</sup> physiologic studies show that the quantity of blood carried by the ovarian veins increases more than 60 times by the thirty-sixth week of pregnancy as compared to the nonpregnant state. Concomitantly the venous pressure in these channels nearly trebles. Under stress of labor, manipulation, or disease one or more of the vessels may rupture.

According to anatomic studies made by Notkovich,<sup>4</sup> the adrenal-renal venous blood supply may intercommunicate with one another as well as with the ovarian veins. We are of the opinion this was the situation in our patient.

The abruptio placentae in our case was probably secondary to the venous pressure built up distal to the vein ruptures. We presume that the mechanism is similar to the situation produced by compressing the vena cava directly and causing retroplacental hemorrhage.<sup>3</sup>

### Summary and Conclusions

A case history is given of a gravid patient who had multiple hemorrhages from the right ovarian and suprarenal venous plexuses.

A collective review from the literature shows that ruptures of the suprarenal or ovarian veins or both during pregnancy or the puerperium are accompanied by acute pain or shock or both, frequently on the right side, often among primigravidas, and frequently associated with a pathologic gestation. The complication is so catastrophic that surgical treatment is mandatory. Untreated, death will usually occur from internal hemorrhage.

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## CASE REPORT OF A PATIENT WITH A TRUE UNICORNUATE UTERUS WITH UNILATERAL RENAL AGENESIS\*

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CONGENITAL anomalies of the genitourinary tract in the female are now found with more frequency than heretofore because of the more widespread use of the uterosalpingogram and the intravenous pyelogram.

True unicornuate uterus, on the other hand, is a comparatively rare condition. It may be suspected if there is agenesis of a kidney and ureter because of the frequent association of these congenital anomalies, but it can be proved only by operation. In 1938 Shumacker<sup>1</sup> reported 28 cases of true unicornuate uterus with unilateral renal agenesis. Since then, 5 more cases have appeared in the literature. With the new case being presented the total becomes 34.

Of all reported cases, there were only 3 in which there was a total absence of ovary, Fallopian tube, round ligament, broad ligament, kidney, and ureter, and it is remarkable that all of these occurred on the left side. Dannreuther<sup>2</sup> reported in 1923 a case of a woman 25 years of age with a true unicornuate uterus and renal agenesis. This was followed by a report by Varino and Beacham<sup>3</sup> in 1940 of the same type. Their patient had a cystic ovary and had borne two full-term infants. Alexander,<sup>4</sup> in 1947, also reported a similar case with a ruptured Graafian follicle of the developed ovary. This patient had borne a full-term living child. A review of the literature showed that only 2 of these patients had cystic ovaries, the first reported by Guthrie and Wilson<sup>5</sup> in 1909 and the other by Varino and Beacham.

The case we are presenting is of special interest because of an associated endometrioma on the developed side.

Mrs. E. S., aged 38 years, when first seen complained of irregular menstrual periods with spotting between periods. The periods were accompanied by cramps which had become increasingly severe in the past year. She also complained of a full feeling in the lower right part of the abdomen with pain at the time of the periods. This also had become progressively worse.

Upon physical examination there was noted in the lower right quadrant a palpable tumor irregular in contour and about 3 cm. above the symphysis. Pelvic examination disclosed a corpus uteri irregular in contour, displaced to the left, and enlarged to the size of a 2 months' pregnancy. A tumor mass was also palpable anterior to the uterus, rising above the symphysis. This was regarded as possibly an ovarian cyst about 7 by 5 cm. in size.

\*Presented at a meeting of the New York Obstetrical Society, Feb. 12, 1957.

TABLE I. DATA ON CASES OF TRUE UNICORNUATE UTERUS WITH UNILATERAL RENAL AGENESIS REPORTED SINCE 1938

CASE	AUTHOR	UTERUS UNI- CORNIS	RENAL AGENESIS	URETER ABSENT	ADNEXA ON DE- VELOPED SIDE	ADNEXA ON DEFEC- TIVE SIDE	AGE
1	Alexander <sup>4</sup>	Right	Left	Left	Ruptured Graafian fol- licle, right ovary	Ovary, tube, round ligament, broad ligament, kidney, and ureter absent	23
2	Daro, Gollin, and Nora <sup>6</sup>	Right	Left	Left	Normal	Left ovary present on pelvic brim. Short Fallopian tube attached to ovary. Thin broad ligament. Left kid- ney and ureter ab- sent	22
3	Daro, Gollin, and Nora <sup>6</sup> from records of 1,000 postmortems (1929-1948)	Left	Left	Left	Hypoplasia of ovaries and left tube	Agenesis of left kid- ney and ureter; agenesis of right Fallopian tube and cervix. Hypoplasia of ovaries and left tube. Uterus uni- cornis, right solid. Atresia of vagina	48
4	Tucker and Baker <sup>7</sup>	Right	Left	Left	Normal	Ovary, Fallopian tube, left kidney, and ureter absent	28
5	Frost (this report)	Right	Left	Left	Normal Fal- lopian tube. Endometrioma, cystic endo- metriosis of right ovary	Left ovary, left tube, round ligament, broad ligament, uterine artery, kid- ney, and ureter ab- sent	39

Operation was undertaken on April 6, 1955. As the abdomen was opened through a right paramedian incision, a large right ovary was found in the median line, about the size of a small orange and containing chocolate-colored material. The uterus, which was definitely enlarged, was found pulled to the right against the wall of the pelvis. The round ligament on the right side was found to be short, about two inches in length. On examination of the left side, no ovary, broad ligament, round ligament, or tube was found.

A total hysterectomy and right salpingo-oophorectomy and appendectomy were carried out. During the course of the procedure, the right uterine artery was exposed and cut, but on the left side no uterine artery was found. Examination revealed the right ureter and right kidney, which seemed large and rather lobulated. No ureter or kidney was palpable on the left side.

*Pathological Report.*—The uterus with cervix attached measured 9.0 by 4.0 by 3.5 cm. The right tube and cystic ovary were attached, but there was no recognizable left ovary, left Fallopian tube, left round ligament, or left broad ligament. The endometrial cavity was abnormal only in that there was no opening for a Fallopian tube on the left. The right ovary measured 7.5 cm. in diameter and was multicystic. The largest cyst was 5 mm. in diameter and filled with a turbid straw-colored fluid. Smaller cystic areas contained hemorrhagic semisolid material.

The final pathologic diagnosis was leiomyoma of the uterus, endometriosis of the right ovary, congenital absence of the left Fallopian tube, left round ligament, left ovary, left broad ligament, and left uterine artery and vein.

After recovery from the operation, the patient was studied by intravenous pyelography. This showed a large right kidney with prompt excretion of dye in good concentration. The right ureter was well outlined and there was no evidence of obstruction. The left renal shadow was absent. The bladder was remarkable for the absence of the left side of the trigone with no left urethral orifice.

### Summary

Three cases of true unicornuate uterus have been reported in the literature. A new case associated with unilateral renal agenesis is described.

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### Discussion

DR. WALTER T. DANNREUTHER.—I have had occasion twice to write a short paper on anomalies of the uterus, one in 1923 and another in 1927, both published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. Since another 30 years have passed, there has not been an opportunity to review my entire experience in detail on such short notice except from the statistical standpoint. I now find that I have had a total of 74 cases of congenital anomalies of the female pelvic organs, including 25 of the uterus, 6 of the ureters, 34 of complete or partial aplasia of the vagina, 3 of phimosis of the cervix, 2 of a solitary ectopic kidney in the pelvis, 2 of hermaphroditism, 1 of supernumerary urethra, and 1 of exstrophy of the bladder.

In the 25 cases of uterine anomalies, practically every variety of developmental defect is represented. In cases of true uterus duplex unicollis, the bladder will be found draped between the two corpora and fused posteriorly with the visceral peritoneum; so in operating on these patients one must be extremely careful not to excise a small section of the bladder in this area. There were 6 ureteral anomalies, either duplicate or unilateral, and concomitant anomalies in the urinary tract should always be looked for in cases of uterine developmental defects.



## TOTAL COLPECTOMY IN THE TREATMENT OF A CASE OF IRREDUCIBLE UTERINE PROCIDENTIA\*

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**A**MONG the many operative procedures for uterine procidentia, total colpectomy is rarely used. Nevertheless, there are certain situations in which this seemingly formidable operation is the best procedure.

Martin<sup>1</sup> in 1920 recommended total colpectomy in cases of procidentia, although the procedure appears to have been previously carried out. In 1925, Dujarier and Larget<sup>2</sup> described their technique of colpectomy and reported 15 successfully treated cases. Phaneuf<sup>3</sup> reported 5 cases in 1935 and emphasized the ease with which such a procedure could be done, even in elderly women, occasionally under local anesthesia alone. In the same year, Rubovits and Litt<sup>4</sup> reported one case performed by a slightly different technique. Lima,<sup>5</sup> discussing the merit of colpectomy in 1943, repeated Phaneuf's statements and gave the same indications for the procedure. In 1950, Williams<sup>6</sup> added 60 cases of his own, and emphasized the importance of uniting the pubococcygeal muscles in the midline. Adams<sup>7</sup> reported 30 operations from 1937 through 1951 with excellent permanent results. These authors were almost all unanimous on certain points:

1. The procedure is especially valuable in cases of inversion of the vagina after hysterectomy and in cases of very large prolapse.
2. It can be performed in elderly women who may be bad surgical risks, under local or spinal anesthesia, with a minimum of operative shock.

### Case Report

Mrs. D. R. (Case Hist. No. E48567), an 81-year-old nulligravida, was admitted to St. Vincent's Hospital on Dec. 29, 1956. The chief complaint was uterine procidentia and urinary incontinence of long duration. She had been totally bedridden for the past several weeks and complained of extreme weakness.

Ten years after the menopause, which had occurred at the age of 42, an abdominal operation was performed because of uterine descensus. Despite this operation the uterus again gradually descended, and the prolapse had been completely irreducible for more than a year.

Physical examination showed an emaciated woman with pulmonary and cardiovascular changes consistent with her age.

Pelvic examination disclosed a markedly thickened, edematous, macerated, and, in some areas, ulcerated vaginal mucosa, which was completely everted, forming a mass approximately

\*Presented at the Residents' Meeting of the Obstetrical and Gynecological Section of the New York Academy of Medicine, May 28, 1957.

10 inches long and 6 inches in diameter. At the apex of the mass, a small opening indicated the external cervical os. A large enterocele, as well as the completely prolapsed urinary bladder, were apparently the chief constituents of the mass. All attempts at reduction on admission remained unsuccessful.

The blood count and the blood chemistry determinations were within normal limits. Excretory urograms demonstrated the almost complete prolapse of the bladder and the presence of vesical and probably renal calculi. X-rays of the chest showed marked pulmonary fibrosis; some left ventricular enlargement, and elongation of the aorta.

It was decided to treat the patient palliatively in the hope of improving the general condition and of reducing the vaginal edema. The regimen consisted of bed rest in slight Trendelenburg position, boroglycerin applications to the mass, and a high-protein, high-vitamin diet. After three weeks her general condition showed marked improvement, but the prolapsed mass had decreased only slightly in size. The urinary incontinence was paradoxical in character, i.e., the urine leaked through the stenosed urethra only under pressure on the distended bladder. When all attempts at replacement had proved futile, it was decided to treat the condition surgically.

Under spinal anesthesia, later supplemented by general inhalation anesthesia, a longitudinal incision was made along the anterior vaginal wall from the external urethral meatus to the external cervical os. The cervix was mobilized and a high amputation carried out and the cul-de-sac was entered. A vaginal cystotomy was then carried out, the vesical calculus, 4 cm. in size, was removed, and the bladder closed with two layers of Atraumatic chromic No. 2-0 sutures.

At this point it was thought that the tissue had been sufficiently mobilized and reposition was attempted, but again without success. Mobilization of the vaginal wall was therefore continued until the introitus was reached. At this stage, replacement was finally successful. Several purse-string sutures were successively placed and the structures gradually elevated. The available musculofascial structures, particularly the pubococcygeal muscle, were approximated in the midline. The entire vaginal wall was finally removed with the preservation of only a small margin used for closing the introitus. A Foley catheter was inserted into the bladder and a Penrose drain placed into the vaginal wound.

The postoperative course was uneventful. The patient was allowed out of bed on the fourth day. When the Foley catheter was removed on the sixteenth day, the patient was able to void spontaneously, with only a small amount of residual urine for the first week thereafter. The excretory urogram showed a decrease in the diameter of the hydro-ureters and a normal intrapelvic position of the bladder. The patient was discharged on the thirty-fourth postoperative day in good condition. She was seen again 3 months after her discharge, well and alert, and in complete control of bladder function.

### Comment

Cases of irreducible procidentia are extremely rare and only isolated cases were reported in the world literature.<sup>8-10</sup> In 1898, Beyea<sup>8</sup> reported a case of "acute septic infection and strangulation of a completely prolapsed uterus" in a 22-year-old para iv, with the prolapse irreducible for 4 years. Vaginal hysterectomy was performed, but the patient died of peritonitis. Jaschke<sup>9</sup> discussed the rarity of irreducible prolapse and concluded that such patients usually succumb either untreated or when an attempt is made to perform hysterectomy. Holden, in a discussion of the report by Phaneuf,<sup>3</sup> stated that he had seen 4 cases, 3 of which had terminated in sepsis, in spite of treatment. In 1938, Frank<sup>10</sup> reported a case of "irreducible, strangulated, complete prolapse of the uterus, complicated by sliding hernia of the cecum and intestinal obstruction" in a 42-year-old para ii. This patient finally recovered after a preliminary abdominal operation for the obstruction, and an eventual cure of the prolapse by a parametrial fixation operation.

After this review of the literature, it seems that our case is the first of irreducible procidentia in which cure was effected by total colpectomy, and permanent relief obtained in a one-stage procedure. This case presents an additional interesting feature in that the patient was a nulligravida. The vaginal cystotomy is to be noted as a proper and successful approach to a vesical calculus when certain indications are present.

### Summary

A case of irreducible vaginal procidentia in an 82-year-old nulligravida is presented. Total colpectomy with high cervical amputation was carried out with a good final result.

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## OBTURATOR NERVE PARALYSIS FROM RADIOACTIVE GOLD

### Report of a Case Following Injection for Carcinoma of the Cervix

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**I**RRADIATION of the parametrium with radioactive colloidal gold is an acceptable method of treatment of carcinoma of the cervix.

The following case report is submitted because of the occurrence of injury to the obturator nerve with loss of motor function in the area of its innervation in a patient who received colloidal gold by transvaginal injection. There are no reports in the literature of such an eventuality following this method of treatment.

D. V. (No. 738246), a 39-year-old white woman, was first seen at Henry Ford Hospital on Dec. 9, 1953. She had a history of rheumatic fever and was in mild congestive failure secondary to mitral stenosis. Mitral commissurotomy was performed on Feb. 15, 1954.

On April 24, 1955, a biopsy of an exophytic lesion of the cervix was performed. A diagnosis was made of squamous-cell carcinoma of the cervix, League of Nations Stage I. In consideration of the cardiac status of the patient, it was elected to treat her with radium and radioactive colloidal gold. Radical hysterectomy was not advised. On April 29, 1955, with cyclopropane anesthesia, 90 mg. of radium was inserted in the cervix with an Ernst applicator, and 4,500 mg. hr. was given.

On May 12, 1955, with low spinal anesthesia, 70 c.c. of radioactive colloidal gold, standardized to contain 100 mc., was injected in a manner comparable to that described by Sherman, Bonebrake, and Allen.<sup>1</sup> A No. 22 gauge spinal needle was inserted lateral to the cervix on the right side through the broad ligament until the iliac bone was encountered. Fifteen cubic centimeters of radioactive colloidal gold was injected in the area as the needle was withdrawn to prevent pooling. A second injection of 10 c.c. was made in the paraureteral region. Finally, 10 c.c. was injected near the obturator foramen. The same procedure was carried out on the left side.

Within one or two days after the administration of the radioactive colloidal gold, she complained of pain in the buttocks, pain on defecation, and aching in both thighs and the calves of both legs. She noticed some incontinence of urine.

On subsequent progress visits at 3 to 4 week intervals, she continued to complain of pain in the buttocks, posterior aspects of both thighs, and lower legs, urinary incontinence, constipation and pain on defecation, with tingling paresthesias intermittently about the anus. She was treated with antispasmodics, analgesics, and cortisone. The latter was given to minimize the fibrotic reaction produced by radiation. She also received medication for her cardiac condition and was permitted to return to work in an automobile plant on Sept. 19, 1955.

On Oct. 9, 1955, the patient was seen because of persistent back and leg pain and coccygodynia. She mentioned unsteadiness of gait with a tendency to fall to the right. The Romberg test was negative. There was tenderness on palpation and percussion over the lumbosacral region. An area of hypoaesthesia about the anus was noted. The left

Achilles tendon reflex was markedly diminished as compared to that on the right. Vibratory and position sense of the legs was normal. There was no evidence of metastases in the spine on x-ray examination. Cystometrogram was normal and there was no residual urine. The myelogram and serologic examination of the spinal fluid were negative. There was no evidence of recurrence of malignancy in the pelvis. The intensity of back and leg pain subsided with bed rest.

The patient was followed in the Out-patient Clinic at 3 to 4 week intervals. She complained of a persistent sensation of pressure in the rectum with inability to have a bowel movement except with weekly enemas. A barium enema examination showed lack of distensibility of the rectum. Proctoscopic examination was negative. She continued to have incontinence.

On July 27, 1956, she complained again of a tendency to fall to the right. Examination of the musculoskeletal system showed almost complete loss of adductor power of the left leg with partial loss of the right. Flexor muscles of the left thigh were also weak. There was pronounced atrophy of the adductor muscle group of the left thigh.

Neurological examination on Aug. 14, 1956, disclosed hypoesthesia over the toes and lateral aspect of both feet, lateral and posterior aspects of the legs and thighs. Weakness and atrophy of the adductor muscles was verified.

When she was seen on Nov. 21, 1956, atrophy of the adductor muscles of the left thigh was unchanged. Pelvic examination on March 9, 1957, showed no evidence of recurrence of the malignancy. Atrophy of the vagina secondary to radiation was evident.

### Comment

The patient sustained obvious damage to both obturator nerves which arise from ventral divisions of the second, third and fourth lumbar nerves.<sup>2</sup> In the lesser pelvis, the obturator nerve runs along the lateral wall in front of the obturator vessels to the obturator foramen. A cross section of the pelvis shows the obturator nerve in the same frontal plane as the ovary.<sup>3</sup> It courses between the ovary and the iliac bone. In accordance with the operative note in this case, it is very likely that radioactive material could have been injected into, or in very close proximity to, the obturator nerves as they cross the lateral pelvic wall. It is also possible that the injected gold was transported in lymphatic channels to obturator lymph nodes in the obturator fossae in amounts sufficient to produce nerve injury.

Allen, Sherman, and Arneson<sup>4</sup> indicated that many of their patients complained of aching pain in the hips, low back, and legs. These symptoms usually subsided in 2 or 3 weeks, although the neuritic pains persisted for 4 to 5 months in a few patients. Eighteen months after the injection of radioactive gold, the patient concerned in this report had clinical evidence of permanent nerve damage manifested by atrophy of the adductor muscles of the left thigh and weakness in the right.

Very little has been reported in the literature concerning the action of x-rays or radium on peripheral nerves. It is well known that nerve tissue is quite insensitive to radiation. However, injection of radioactive gold directly into or in close proximity to the obturator nerve would produce focal radiation of far greater intensity than would result from any presently available form of x-ray or intracavitary radium application.<sup>4</sup>

The mucosa of the rectum and bladder are very radiosensitive. Although the radium was inserted in this instance with the usual care and the position



of the applicator was checked by x-ray, one cannot exclude this modality as a cause of the rectal and bladder symptoms of this patient.

It is conceivable, though quite unlikely, that trauma from the needles used was of etiological significance.

### Conclusions

1. From this case report, it is apparent that a permanent injury to the obturator nerve can occur following the injection of radioactive gold.
2. Injection of radioactive material should be made with consideration of major nerves and other vital structures.
3. Patients with symptoms of neuritis following the injection of radioactive materials should have orthopedic and neurological examinations.

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## Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

### REVIEWS OF NEW BOOKS

**Human Generation.** By Arthur W. Meyer. 143 pages. Stanford, Calif., 1956, Stanford University Press. \$3.50.

**Pioneer Surgeons of the Woman's Hospital.** By J. P. Marr. 148 pages. Philadelphia, 1957, F. A. Davis Company. \$5.50.

Two small but priceless gems are presented for all who value the rich historical background of knowledge of human reproduction and the surgical specialties concerned therewith.

Meyer has furnished an accurate translation of Von Baer's *Commentary on the Writing on the Eggs of Mammals and Man*. Perusal of this document will at once reveal a fundamental contribution of great import. It has to some extent been overshadowed by the *Epistle* which, although appearing later, was intended to be the primary announcement of the genesis of mammalian and human eggs.

As background the author has furnished fascinating biographical material dealing with the salient aspects of Von Baer's life. Short biographical sketches and translations of the outstanding embryological contributions of Karl Friedrich Burdach and of Johann Josef Ignatz von Döllinger precede the notes on Von Baer and his teachers. While their ideas must have had great influence on him, the translations reveal their works to be but slightly based on observation. Nevertheless, this is the background from which Von Baer drew stimulus and inspiration.

Under the title *Pioneer Surgeons*, Marr presents brief biographical sketches of the four leaders of American gynecological surgery associated with the founding and development of the Woman's Hospital in New York. The lives of the first two, Sims and Emmet, are oft told and familiar, of Thomas Gaillard Thomas and Edward Randolph Peaslee not so much is known. These are sketches done with loving care by a man devoted to a great hospital and its traditions. They are nicely illustrated and furnish in continuity the history of some of the early steps and difficulties of American gynecology.

**Gynecologic Therapy.** By William Bickers. 158 pages. Springfield, Ill., 1957, Charles C Thomas, Publisher. \$4.25.

As a short book of 158 pages, including the index, written for the intern and resident in order to assist them in making a diagnosis and instituting treatment, this monograph is eminently successful. The contents cover the entire range of gynecology and are well arranged for ready reference. The language is concise but nevertheless extremely descriptive. Words are not wasted. The author is succinct and direct and conveys the impression that his answers are correct. Indeed, to the more experienced reader of gynecological

literature the same feeling is given. Although he may occasionally find himself in disagreement with the author, he is repeatedly amazed and delighted to discover affirmation of his own point of view.

The major emphasis of the book, as its title implies, is on therapy. Whether the ailment is carcinoma or pruritus vulvae, enterocele or menstrual irregularity, the same thoroughness is used. Treatment is practical and well outlined. Names of drugs together with dosage are clearly stated, while the main principles involved in operative procedures are described lucidly and simply. In addition, the author concerns himself with abnormal physiology, pathology, anatomy, embryology, and endocrinology. All are integrated into the pattern of the book in so unobtrusive a way as to be taken for granted. On analysis, however, it becomes very clear that only a person with tremendous clinical and scientific background could produce such a wealth of correlated information in so few words.

**Abdominal Total Hysterectomy.** By Frank Musgrove. 32 pages, 18 plates. Springfield, Ill., 1957, Charles C Thomas, Publisher. \$2.25.

An unusual technique for performance of abdominal hysterectomy is presented in a concise manner in this small book. This technique was first presented to the Royal Society of Medicine, London, 1955. If the line drawings at times leave something to the reader's imagination, the text compensates for it in clarity.

The stated purposes in devising one more operative method are: to surmount the technical difficulties due to the position of the uterus; to reduce the possibility of injury to the bladder and ureters; to facilitate closure of the vaginal cuff and prevent postoperative prolapse of the vault. The first aim is fulfilled by mobilizing the uterus early in the course of the operation, the second by doing what has long been strictly avoided by gynecologists—introducing a finger into the vagina after opening the posterior cul-de-sac from above, in order to support the bladder with the vaginal hand while the other hand strips the bladder off the lower segment and cervix under direct vision. The third aim is accomplished by the use of specially devised clamps which clamp the cervical cuff, and by securing the cuff to the preserved uterosacral ligaments and the remainder of the cardinal ligaments.

The author says that, in spite of the unorthodoxy of introducing one finger into the vagina, he has not had a case of "clinical peritonitis" in 1,000 hysterectomies of this type. Bacteriological studies on the vaginal flora prior to and after preparation of the vagina were done. No case of "pathogens" was found in cultures made after cleansing, while several were found prior to it. It is unfortunate that the author did not state what he considers a "pathogen." Whether one approves or not of the new method the author shows evidence of excellent descriptive talent.

**Therapeutic Use of Artificial Radioisotopes.** Edited by Paul F. Hahn, 414 pages, 140 illustrations. New York, 1956, John Wiley & Sons, Inc. \$10.00.

**Clinical Use of Radioisotopes.** By W. H. Beirwaltes, P. C. Johnson, and A. J. Solari. 456 pages, 117 figures. Philadelphia, 1957, W. B. Saunders Company. \$11.50.

These two excellent books cover much of the same ground but the latter (*Clinical Use of Radioisotopes*) has the advantage of having been written by a team engaged in teaching the subject to physicians and medical students, while the former is a collection of 19 chapters contributed by an international array of authors.

While both books provide some background in nuclear physics, dosimetry, biologic effects of radiation, and the essentials of setting up an isotope laboratory, the latter is better adapted to the needs of newcomers to the field. In general, both books give more space to the use of  $I^{131}$  in thyroid disorders than to any other single topic. Other isotopes that are used clinically receive attention in rough proportion to the popularity of their use.

**Biochemical Contributions to Endocrinology.** By Charles Dodds. 76 pages, 28 illustrations. Stanford, Calif., 1957, Stanford University Press. \$3.00.

This small book comprises the five lectures given by the author in 1956, at the Medical School of Stanford University.

To a large degree, the book is a historical outline of the study of endocrinology, but some of the clinical applications are described. Especially interesting are the two chapters on the agricultural applications of the hormones, particularly estrogen and the discovery of aldosterone. The latter is of interest because of its newness.

There is nothing very outstanding about the book, however, and it offers very little for the clinician.

**Die Pathogenese des Morbus haemolyticus neonatorum (The Pathogenesis of Hemolytic Disease of the Newborn).** By G. Martius. 70 pages. Stuttgart, 1956, Georg Thieme Verlag. (In the United States, New York, Intercontinental Medical Book Corp.) \$2.30.

This book is divided into two almost equal parts. The first section reviews critically, at length and in some detail, the previous literature on the pathogenesis of hemolytic disease of the newborn and discusses the present knowledge on antigen and antibody transfer across the placenta. It is particularly emphasized that antigens of the ABO system are not present in the blood-free placenta.

The second section deals largely with a group of experiments which are well covered by controls which show that:

1. Conglutinating anti-Rh sera do not react with placental tissue of Rh-positive infants.
2. Agglutinating anti-Rh sera undergo nonspecific reactions unrelated to Rh antigens.
3. There is no Rh antigen in the umbilical cord or in the serum of Rh-positive subjects.

In histologic examination of erythroblastotic placentas the author found evidence of disease only in the stroma, based on intravascular reaction of antibody and antigen. The persistence of two layers of epithelium is considered to be a lack of aging. The following conclusions are drawn:

1. There is no Rh antigen in the placenta.
2. The healthy placenta, in the absence of trauma, is a barrier to sensitization of the mother. However, trauma to placental vessels is always present at the time of labor and delivery.
3. The erythroblastotic placenta permits fetal erythrocytes to cross to the maternal blood stream, giving a reinforcing reaction and, hence, rising antibody titers.
4. Minimal (0.5 c.c.) blood administration is enough to sensitize the mother.

The material is presented with great clarity and it would appear that the experimental techniques were rigorously exact.

**Textbook of Gynaecology.** By K. M. Masani. Second edition. 775 pages, 276 figures. Bombay 7, India, 1957, Popular Book Depot.

A second edition of Masani's *Textbook of Gynaecology* is complete, authoritative, and written in a very agreeable, simplified, concise manner which should appeal to the reader. The author has retained much of the basic material of the original text but has elaborated more thoroughly on many entities and has added all the newer aspects of gynecologic disease in the present edition. In addition to the usual gynecologic entities, it covers the related subjects such as anatomy, embryology, physiology, endocrinology, and psychology. As in the previous edition the author has laid special emphasis on clinical diagnosis and

treatment. Differential diagnosis has been given in detail to avoid pitfalls in clinical work. The differences in clinical gynecology in Western countries and in India and generally in other Eastern countries have been emphasized. The author provides wide coverage of the subject in 14 major sections, 52 chapters, and 775 pages.

An excellent feature of the book is a short historical account given as a preface to all major subjects discussed. The section on "History and Examination" emphasizes diagnostic aids and cancer detection, including cytology. The presentation of subjects is orderly and detailed. The reviewer is particularly impressed with the section on applied physiology in which a composite account is given of the different epochs of a woman's life. The author has paid particular attention to the psychological considerations in gynecologic practice. He devotes a chapter to the orientation of the gynecologist to the impact of social, psychological, and environmental factors in the causation of some of the disorders commonly seen in his practice. Carcinoma of the cervix is particularly well handled and is thoroughly discussed, especially the chapters dealing with the various techniques and results of radium therapy and irradiation versus surgical treatment. There is a section on operative gynecology in which the techniques of the most common procedures are given in detail. Pre- and postoperative care is also discussed.

Although gynecologic pathology has not been emphasized in this text, the author includes enough basic information to meet the minimum requirements of undergraduate students. Unfortunately, many of the photographic illustrations are indistinct, and perhaps the author should provide more and better illustrations in the future editions. Many diagrams, however, particularly those illustrating the steps of operations, adequately supplement the written material. In most sections of the book, the author has provided a satisfactory bibliography of important contributions at the end of each chapter, for graduates appearing for higher examinations and practitioners who desire to read in detail some of the advanced aspects of the subject. Certain subjects, however, are inadequately documented with current reference material.

These points are minor in an otherwise excellent book, but perhaps they should be mentioned. Although there are a few scattered typographical errors, the text should be acceptable to the severest critic.



## BOOKS RECEIVED FOR REVIEW

- Les Accidents renaux de la grossesse et de l'avortement.** By D. Alagille, A. Bonis, J. Cronier, D. Fritel, F. Lepage, J. Levy, R. Merger, J. P. Mery, P. Milliez, C. Nezeloff, and G. Richet. 60 pages. Paris, 1957, Masson & Cie.
- Acquisitions récentes en cytologie vaginale.** By J. Paul Pundel. 236 pages, 62 figures, 15 tables. Paris, 1957, Masson & Cie.
- Atlas der Kolpomikroskopie.** By Tassilo Antoine and Viktor Grunberger. 244 pages, 176 tables, 181 illustrations. Stuttgart, 1956, Georg Thieme.
- Biochemical Contributions to Endocrinology.** By Charles Dodds, 76 pages, 28 illustrations. Stanford, Calif., 1957, Stanford University Press. \$3.00.
- Biologic Basis of Cancer Management.** By Freddy Homburger, 354 pages, 39 tables, 10 figures. New York, 1957, Hoeber-Harper. \$10.00.
- Clinical Use of Radioisotopes.** By Theodore Fields and Lindon Seed. 455 pages, 70 figures, 27 tables. Chicago, 1957, The Year Book Publishers, Inc. \$9.50.
- Etiologic Factors in Mental Retardation.** Twenty-third Conference, Ross Pediatric Research Conference, Columbus, Ohio, 1957.
- The Function of the Ureter and Renal Pelvis.** By Fredrik Kiil. 205 pages, 16 figures. Philadelphia, 1957, W. B. Saunders Company. \$7.50.
- Headache—Diagnosis and Treatment.** By Robert E. Ryan. Second edition, 421 pages. St. Louis, 1957, The C. V. Mosby Company. \$6.75.
- Human Cancer.** By M. M. Black and F. D. Speer. 273 pages, 34 figures, 15 tables. Chicago, 1957, The Year Book Publishers, Inc. \$7.50.
- Hypnosis in Medicine and Surgery.** By James Esdale. 259 pages. New York, 1957, Julian Press. \$4.00.
- Introduction to Anesthesia.** By R. D. Dripps, J. E. Eckenhoff, and L. D. Vandam. 266 pages, 47 figures. Philadelphia, 1957, W. B. Saunders Company. \$4.75.
- Introduction to Clinical Endocrinology.** By A. Stuart Mason. 192 pages, Springfield, Ill., 1957, Charles C Thomas, Publisher. \$4.50.
- Methodology of the Study of Ageing.** By G. E. W. Wolstenholme and C. M. O'Connor. Vol. 3, 202 pages. Boston, 1957, Little, Brown & Company. \$6.50.
- Modern Perinatal Care.** By Leslie V. Dill. 309 pages, 51 figures. New York, 1957. Appleton-Century-Crofts, Inc. \$6.50.
- Occipito-posterior Positions.** By Edward L. King. 106 pages, 60 figures. Springfield, Ill., Charles C Thomas, Publisher. \$3.75.
- Operative Obstetrics.** By R. Gordon Douglas and William Stromme. 735 pages, New York, 1957, Appleton-Century-Crofts, Inc. \$20.00.
- Spontaneous and Habitual Abortion.** By Carl T. Javert. 450 pages, 196 illustrations. New York, 1957, McGraw-Hill Book Company, Inc. \$11.00.
- Textbook of Gynaecology.** By K. M. Masani. Second edition, 775 pages, 276 illustrations. Bombay, 1957, Popular Book Depot. Rs 25/
- Trophoblastic Growths.** By J. Smalbraak. 342 pages, 66 plates, 9 tables. Princeton, 1957, D. Van Nostrand Company, Inc. \$12.75.

## SELECTED ABSTRACTS\*

### Journal of the American Medical Association

*Vol. 165, September 14, 1957.*

\*Kaltreider, D. F.: Fetopelvic Grading of Breech Presentations, p. 132.

\*White, M. A., Prout, C. T., Fixsen, C., and Foundeur, M.: Obstetrician's Role in Postpartum Mental Illness, p. 138.

**Kaltreider: Fetopelvic Grading of Breech Presentations, p. 132.**

The author presents excellent and useful criteria in the management of breech presentations. The obstetrician must face the decision whether to deliver vaginally or by cesarean section. Consideration of the size of the pelvis determined clinically and by x-ray pelvimetry, the shape of the pelvis, and the weight of the fetus are factors entering into this consideration. Each patient is graded from 0 to 8 according to the favorability of the above combination.

ROBERT C. KNAPP

**White, Prout, Fixsen, and Foundeur: Obstetrician's Role in Postpartum Mental Illness, p. 138.**

This article is concerned with the finding that postpartum mental illness is not a psychic entity. The authors draw this conclusion from a comparison between 100 patients with postpartum mental illness and 100 female patients of the same age who were admitted for mental illness that did not precede childbirth. No significant difference was manifested in the symptoms of the two groups and no particular etiology is associated with postpartum mental illness. The authors feel that it is merely a manifestation of the usual mental diseases in unstable people in whom childbirth is only the final precipitating factor.

The article calls for a revision of this subject in obstetrical texts and devotes a few remarks to the need for early diagnosis on the part of the obstetrician and for the provision of nursing care.

ROBERT C. KNAPP

### The Journal of Clinical Endocrinology and Metabolism

*Vol. 17, September, 1957.*

Barr, R. W., and Sommers, S. C.: Endocrine Abnormalities Accompanying Hepatic Cirrhosis and Hepatoma, p. 1017.

Greer, M. A., and Shull, H. F.: Quantitative Study of Effect of Thyrotropin on Thyroidal Secretion Rate in Euthyroid and Thyrotoxic Subjects, p. 1030.

Sandberg, A. A., and Slaunwhite, W. H., Jr.: Differences in Metabolism of Prednisolone-C<sup>14</sup> and Cortisol-C<sup>14</sup>, p. 1040.

Migeon, C. J., Keller, A. R., Lawrence, B., and Shepard, T. H.: Dehydroepiandrosterone and Androsterone Levels in Plasma. Effect of Age and Sex; Day to Day and Diurnal Variations, p. 1051.

Finkelstein, M., and Goldberg, S.: Test for Qualitative and Quantitative Estimation of Pregnane-3 17, 20-Triol-11-One in Urine: Significance in Adrenal Disturbances, p. 1063.

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\*Titles preceded by an asterisk are abstracted below.

- Caren, R., and Corbo, L.: Pyrimidine Metabolism in Diabetes Mellitus Studied With the Uracil Tolerance Test, p. 1071.
- Imanaga, H., Kondo, T., and Mori, I.: Inactivation of Antidiuretic Substances by Human Liver, p. 1081.
- \*Hilf, R., and Rosen, I.: Effect of Re-use of *Rana Pipiens* Upon Accuracy of the Pregnancy Test, p. 1088.
- Harell-Steinberg, A., Ziprkowski, L., Haim, S., Gafni, J., and Levin, M.: I. Exfoliative Dermatitis as the Presenting Sign of Hypoparathyroidism, p. 1094. II. Inactivation of Parathyroid Hormone in a Case of Clinical Hypoparathyroidism, p. 1099.

**Hilf and Rosen: Effect of Re-use of *Rana Pipiens* Upon Accuracy of the Pregnancy Test, p. 1088.**

It has been customary to use the frog *Rana pipiens* only once for the determination of pregnancy. These workers tested 962 frogs. There were 481 pregnancy tests done and many of the frogs were used several times. Twenty-two frogs were used for five tests. The accuracy of the tests was 96 per cent.

There was a great variation in the sensitiveness of the frogs to the chorionic gonadotropin hormone. One hundred per cent of the frogs would react to 40 I. U. of CGH and 25 per cent would react to 10 I. U. There may be false negative tests if they are made at times when the patient is not producing sufficient CGH.

From this work, it appears that *Rana pipiens* may be used as a test animal as many as five times.

J. EDWARD HALL

**The Lancet**

Vol. 1, June 22, 1957.

- \*Gunter, M.: The Transfer of Blood Between Baby and Placenta in the Minutes After Birth, p. 1277.
- \*Saltoun, D., and Kinn, D. D.: Acute Suppression of Urine and Liver Failure Accompanying Eclampsia, p. 1280.

**Gunter: Transfer of Blood Between Baby and Placenta in Minutes After Birth, p. 1277.**

With the use of a semiautomatic, continuously recording weighing machine, the changes in weight were determined in 39 babies born by vaginal delivery and 11 born by cesarean section. If the umbilical cord was left untied, the blood volume of the baby usually increased by a significant amount (range: 0.8 to 4.7 per cent of the body weight). The amount the baby received correlated roughly with the body weight. Size was not the sole determining factor, however. If the placenta was placed lower than the baby, siphonage of blood into the placenta occurred. The continuance of pulsation in the umbilical arteries reduced the flow and the duration of pulsation in the arteries may be affected by the degree of anesthesia of the mother. Furthermore, the intake was limited by a certain sequence of events. In many instances a steep gradient showing a flow into the baby was followed by a burst of crying and the resultant increase in intrathoracic pressure reduced the flow. A most important factor in the flow of blood is the interaction and interdependence of the inflation of the lungs and the increasing circulation in them. Vigorous babies born by cesarean section also gained blood provided the placenta was not held in such a fashion to cause siphonage from the baby. Delay in tying the umbilical cord may be of advantage and the suggestion is made that the incidence of pulmonary syndrome might be reduced if the reservoir is allowed to function fully. Only one of these babies became severely jaundiced.

DAVID M. KYDD

**Saltoun and Kinn: Acute Suppression of Urine and Liver Failure Accompanying Eclampsia, p. 1280.**

A woman, aged 29, developed eclampsia. Following the birth of a stillborn infant, acute suppression of urine, hyperpyrexia, and jaundice occurred. She was treated with 25 and 40 per cent glucose given through a catheter placed in the inferior vena cava by way of the saphenous vein. In addition, she was given sedatives and the high temperature which lasted 3 days was reduced by fans directed over the wet sheet covering the patient. Diuresis began on the fifth day and the jaundice slowly subsided. At no time did the patient develop hyperpotassemia and the acidosis was treated by appropriate amounts of  $\frac{1}{6}$  molar lactate solution. The patient's blood pressure became normal and the renal function improved. When last seen, 4 months after discharge, the specific gravity of the urine was 1.002-1.020 and the standard urea clearance 50 per cent of normal function.

DAVID M. KYDD

*Vol. 2, July 6, 1957.*

\*Berlyne, G. M., Short, I. A., and Vickers, C. F. H.: Placental Transmission of the L.E. Factor, p. 15.

\*Danon, M., and Sachs, L.: Sex Chromosomes and Human Sexual Development, p. 20.

**Berlyne, Short, and Vickers: Placental Transmission of the L.E. Factor. Report of Two Cases, p. 15.**

Two patients with systemic lupus erythematosus who became pregnant were observed. Neither of these patients received any steroid therapy immediately before or during their pregnancies.

One patient, whose disease appeared to be in remission before the pregnancy, developed an increased amount of globulin in the serum, a rash, and a reappearance of L.E. cells in the blood. She improved spontaneously 6 weeks after delivery. The baby appeared to be normal but L. E. cells were found in the peripheral blood up to the age of 7 weeks.

The other patient developed a marked anemia which responded to oral and intravenous iron and marked dyspnea without cardiac enlargement. Occasional L.E. cells were found in the peripheral blood. The baby was normal but L.E. cells were found in the cord blood and in the peripheral blood at the age of 7 days. By the end of the seventh week after delivery, no L.E. cells were found in the infant's blood although they were present in the mother's blood in large numbers at that time.

The first baby was breast-fed for 6 weeks and the second for only one. The L.E. reaction appeared to be more severe in the former baby. At the age of 6 months, both of these babies were perfectly well.

DAVID M. KYDD

**Danon and Sachs: Sex Chromosomes and Human Sexual Development, p. 20.**

Theoretically, 3 sets of causal factors for intersexuality were assumed: (1) genes, presumably single gene mutations (since interracial crosses in man have not been shown to produce intersexes); (2) abnormal distribution of sex chromosomes (XXY, XO, etc.); (3) endocrine dysfunction induced by external factors or by genetic factors affecting the endocrine system. Most of the abnormalities in sexual development are due to failures of the endocrine system, but, by a study of the sex chromosomes, the syndrome of testicular feminization and some instances of gonadal agenesis (Turner's syndrome) were shown to be genetically induced types of intersex possibly caused by abnormal sex chromosome constitution. Also, a gene-induced reversal of sex appears to occur in Klinefelter's syndrome.

The endocrinologically induced types of intersex respond well to therapy with the appropriate hormone, whereas in the genetically induced instances the pituitary gland is paradoxically insensitive to the normal or almost normal androgens and estrogens secreted by the gonads and treatment is unsatisfactory.

Both sexes, though they can secrete the same hormones in the same quantities, are different in their responses because of their genetic constitution. The role of genetic factors may be that of determining the responsiveness of the soma to hormone stimuli.

Cytologic diagnosis of the sex chromosomes, together with anatomic, endocrinologic, and genetic evidence, has made possible a new approach to the study of normal and abnormal human sexual development.

DAVID M. KYDD

*Vol. 2, July 20, 1957.*

\*Medalie, J. H.: Relationship Between Nausea and/or Vomiting in Early Pregnancy and Abortion, p. 117.

**Medalie: Relationship Between Nausea and/or Vomiting in Early Pregnancy and Abortion, p. 117.**

Among 100 pregnant women studied consecutively in rural Israel, 59 were primiparous and 41 multiparous. The ages ranged from 17 to 37. Of these 100 women, 71 per cent had nausea, vomiting, or both, 23 per cent had vaginal bleeding, and 6 per cent had none of these manifestations. Of 52 women who had severe or moderately severe nausea or vomiting, only one had a threatened abortion, whereas among the 48 women who had but mild symptoms there were 11 complete abortions and 11 threatened abortions. No correlation between the woman's age, parity, or period of residence in Israel, and either nausea, vomiting, or abortion was found. The inverse relationship between nausea and vomiting and abortions in the first trimester of pregnancy suggests as yet unknown common factors in their etiology.

DAVID M. KYDD

### **Revista de ginecologia e obstetricia (Brazil)**

*Vol. 100, May, 1957.*

\*Arriagada, A.: A World-Wide Campaign for Diffusion of Knowledge of the Dangers of Multilations on the Normal Route Deliveries and the Convenience of Adopting the Cesarian (sic) Operation as Compulsory, p. 55.

**Arriagada: A World-Wide Campaign for Diffusion of Knowledge of the Dangers of Multilations on the Normal Route Deliveries and the Convenience of Adopting the Cesarian (sic) Operation as Compulsory, p. 55.**

The author expresses a unique opinion. His intentions are well stated by him: "The radical reform in obstetrical conduct which we propose is the most effective and fundamental aid to the mother and to the child and is designed essentially to produce a better society, free of the occult but inevitable ritual multilations which normal birth, via the natural passages, implies, and which is accepted without protest, until today, and which, for the first time in the history of human society, we denounce as injurious, mutilating, and barbaric." He describes the process of birth in animals and compares it to that in humans and concludes that in animals the size of the pelvis is more than ample for the fetal skull, while in humans some compression of the fetal skull, and hence of the fetal brain, must take place. He feels, therefore, that cesarean section eliminates this problem. He also invokes the United Nations declaration of Dec. 10, 1948, which proclaims a "Universal Declaration of Human Rights" and which in substance interdicts torture or cruel treatment to any human being.

FRANCIS B. O'BRIEN





## Correspondence

### Correction on Early Article on Fracture of Pelvis in Pregnancy

*To the Editors:*

The issue of August, 1957, contained an article, "Fracture of the Pelvis in Pregnancy," by N. Mulla, M.D., of Albuquerque, New Mexico, in which the author referred to an article published by me in 1932. I beg to call attention to one or two slight errors.

First, I should like to correct the spelling of my name, which was misspelled "Shuman." I realize that the name *Schuman* with its several variations in spelling appears frequently in the obstetrical-gynecological literature, the most distinguished, of course, being that of Edward A. Schumann, the dean of American gynecologists.

Second, Dr. Mulla, in stating, "While Shuman [sic], after reviewing 170,000 delivery records at the New York Lying-In Hospital," gives the impression that my work was done at the New York institution. The fact is that the cases reported emanated from the Sinai Hospital of Baltimore. The New York statistics were culled as a result of a questionnaire sent to several large obstetrical hospitals and were cited to illustrate the paucity of cases up to 1931.

I was very pleased to read Dr. Mulla's paper, as the subject is a neglected one. My article concerned itself with the effect of an old or previous fracture of the pelvis on a current pregnancy and labor. It was read before the Baltimore Obstetrical and Gynecological Society in January, 1931, and, to my knowledge, was the first report made and published on that subject in this country. However, Ward L. Ekas in May, 1931, reported a case along with other types of deformed pelvis under a different subject title. There have been a few recent articles on the subject, but I have noticed that the authors did not delve very deeply into the literature. I find this to be a common fault in medical writing, and have commented in these pages previously on this failure.

I want to congratulate Dr. Mulla for his thoroughness in "digging up" an article twenty-five years old. I trust he will not mind the corrections made solely for purposes of identity and source of material.

WILLIAM SCHUMAN, M.D.

1716 EUTAW PLACE  
BALTIMORE 17, MARYLAND  
AUGUST 27, 1957

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### Suggested Refinement in Testing Clinical Effects of Placebos Used as Controls

*To the Editors:*

We have strong evidence to indicate that the incidence of side effects in using any preparation (active drugs as well as placebos) is particularly great among the patients in whom the symptomatology has a strong emotional overlay. Thus, placebo effects can be expected to comprise a substantial proportion of side effects encountered in the use of many active drugs.

In order that the physician may be able: (a) to identify and differentiate side effects associated with placebo response from those associated with pharmacological action of the drug used, and (b) to reduce or eliminate placebo effects which interfere with the effectiveness of active drugs, I should like to suggest the following double placebo technique:

1. Two types of placebos should be prepared: (a) a placebo with a repulsive or spectacular appearance, and (b) a placebo identical in appearance with the active drug.

2. Before dosing with the active drug, the physician should prescribe the repulsive placebo.

3. If he gets side effects with the repulsive placebo, he tells the patient that he is now going to replace it with something which will have the same effect, but without nausea, or whatever unpleasant side effects have been complained of. This replacement, of course, is the second placebo.

4. If the second placebo does eliminate the side effects encountered with the repulsive placebo, then our aim to demonstrate the maximum that can be produced through suggestion has been accomplished, and the patient is put on the real drug.

5. If the second placebo fails to eliminate the side effects from the repulsive placebo, or stimulates its own set of effects, at least the physician will be able to recognize their source when he puts the patient on the pharmacologically active drug.

CONRAD CHYATTE, PH.D.

ASSISTANT PROFESSOR OF PSYCHOLOGY

DEPAUL UNIVERSITY  
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CHICAGO 1, ILLINOIS  
SEPTEMBER 3, 1957

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## *Items*

### **American Board of Obstetrics and Gynecology**

The next scheduled examinations (Part II), oral and clinical, for all candidates will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 7 through 17, 1958. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

ROBERT L. FAULKNER, M.D., SECRETARY  
2105 ADELBERT ROAD  
CLEVELAND 6, OHIO

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### **Fifteenth British Congress of Obstetrics and Gynaecology**

The Fifteenth British Congress will be held in Cardiff on July 14, 15, and 16, 1959.

The program will include a symposium on the influence of certain factors in pregnancy and labor on the future development of the child. Among other subjects proposed for discussion are Psychosomatic Gynaecology, Ovarian Malignant Disease, Oestrogen Metabolism, and The Place of Oxytocic Drugs in Obstetrics.

All communications relating to this Congress should be addressed to the Honorary Secretaries, British Congress, Maternity Hospital, Glossop Terrace, Cardiff, Wales.

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January and July)

- American College of Obstetricians and Gynecologists.** (1951) *President*, R. Gordon Douglas, New York, N. Y. *Secretary*, John C. Ullery, P. O. Box 749, Chicago 90, Ill. Next clinical meeting, Hotel Statler, Los Angeles, Calif., April 21-23, 1958.
- American Gynecological Society.** (1876) *President*, Howard C. Taylor, Jr., New York, N. Y. *Secretary*, Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C. Annual meeting, Grove Park Inn, Asheville, N. C., May 19-21, 1958.
- American Association of Obstetricians and Gynecologists.** (1888) *President*, William F. Mengert, Chicago, Ill. *Secretary*, E. Stewart Taylor, 4200 E. Ninth Ave., Denver 20, Colo. Annual meeting, Sept. 4-6, 1958.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Herbert E. Schmitz, Chicago, Ill. *Secretary*, Edwin J. DeCosta, 104 S. Michigan Ave., Chicago 3, Ill. Annual meeting, Hotel Leamington, Minneapolis, Minn., Oct. 2-4, 1958.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, Manly E. Hutchinson, Columbia, S. C. *Secretary*, W. Norman Thornton, Jr., Dept. of Obstetrics and Gynecology, University of Virginia, Charlottesville, Va. Next meeting, Hollywood Beach Hotel, Hollywood, Fla., Feb. 1-5, 1958.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Woodard D. Beacham, New Orleans, La. *Secretary*, Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, San Francisco, Calif., June 23-27, 1958 (at time of annual A. M. A. meeting).
- Society of Obstetricians and Gynaecologists of Canada.** (1944) *President*, George M. White, St. John, N. B. *Secretary*, F. P. McInnis, 280 Bloor St. W., Toronto, Ont. Annual meeting, The Algonquin, St. Andrews-by-the-Sea, New Brunswick, June 19-22, 1958.
- American Board of Obstetrics and Gynecology, Inc.** (1930) *President*, Bayard Carter. *Secretary*, Robert L. Faulkner, 2105 Adelbert Rd., Cleveland 6, Ohio. Next meeting, May 7-17, 1958.
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- Akron Obstetrical and Gynecological Society.** (1946) *President*, B. N. Riddle. *Secretary*, Louis M. Walker, 1108 Second National Bldg., Akron 8, Ohio. Meetings, quarterly.
- Alabama Association of Obstetricians and Gynecologists.** (1940) *President*, Buford Word, Birmingham, Ala. *Secretary*, Julian P. Hardy, 920 S. 19th St., Birmingham 5, Ala.
- Alameda County Gynecological Society.** (1951) *President*, Wilson Footer. *Secretary*, Emery P. Page, 3031 Telegraph Ave., Berkeley 5, Calif. Meetings, fourth Wednesday of each month.
- Arkansas Obstetrical and Gynecological Society.** (1953) *President*, J. W. Kelsey. *Secretary*, Arthur Hope, Fort Smith, Ark. Meetings, April and October.
- Atlanta Obstetrical and Gynecological Society.** (1954) *President*, George A. Williams. *Secretary*, William H. Grimes, Jr., 272 Boulevard, N. E., Atlanta 12, Ga. Meetings, January, April, June, and October.
- Birmingham Obstetrical and Gynecological Society.** (1949) *President*, Ernest B. Oliver. *Secretary*, Eugene Howe, 920 S. 19th St., Birmingham 5, Ala. Meetings, last Thursday in January and March.
- Boston, Obstetrical Society of.** (1861) *President*, Paul A. Younge. *Secretary*, A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, third Monday, January, February, April, October, and November.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, John S. Giaccone. *Secretary*, Sidney S. Steckel, 800 Grand Concourse, New York, N. Y. Meetings, fourth Monday, October, November, January, February, March, and April.

\*Changes, omissions, and corrections must be received by the publisher two months in advance, by May 1 for the July Roster and by November 1 for the January Roster. Please address The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

- Brooklyn Gynecological Society, Inc.** (1890) *President*, Arthur T. Anthony. *Secretary*, Warren A. Lapp, 731 E. 22nd St., Brooklyn 10, N. Y. Meetings, third Wednesday, October, November, January, February, March, April, and May.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, Milton H. Kahn. *Secretary*, Chester Kaminski, 333 Linwood Ave., Buffalo 9, N. Y. Meetings, October through May.
- Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Albert W. Van Ness. *Secretary*, James E. Covell, 753 James St., Syracuse 3, N. Y. Meetings, as announced.
- Chicago Gynecological Society.** (1878) *President*, A. F. Lash. *Secretary*, William G. Cummings, 636 Church St., Evanston, Ill. Meetings, third Friday, October through June.
- Cincinnati Obstetrical and Gynecological Society.** (1876) *President*, Robert R. Pierce. *Secretary*, Edward Alberts, 199 Wm. Howard Taft Rd., Cincinnati 19, Ohio. Meetings, third Thursday, September through June.
- Cleveland Society of Obstetrics and Gynecology.** (1947) *President*, Alwyn E. Bennett. *Secretary*, Richard Glove, 20119 Van Aken Blvd., Shaker Heights 22, Ohio. Meetings, fourth Monday, September, November, January, March, and May.
- Columbus Obstetric-Gynecologic Society.** (1944) *President*, Fred Hapke. *Secretary*, Harry E. Ezell, Jr., 81 S. Fifth St., Columbus, Ohio. Meetings, last Wednesday of month, September through May, except December.
- Connecticut Society of American Board Obstetricians and Gynecologists, Inc.** (1952) *President*, Hugh K. Miller. *Secretary*, Joseph Klein, 435 Farmington Ave., Hartford 5, Conn. Meetings, April and October.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, W. K. Strother, Jr. *Secretary*, H. I. Kantor, 3534 Maple Ave., Dallas 19, Texas. Meetings, spring and fall.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, H. E. McKnight. *Secretary*, Paul G. Seyler, Fidelity Medical Bldg., Dayton 2, Ohio. Meetings, third Wednesday each month.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, W. F. Manly. *Secretary*, Alvin J. Frosh, 2222 East 18th Ave., Denver, Colo. Meetings, first Monday of every month, October through May, inclusive.
- Florida Obstetric and Gynecologic Society.** (1948) *President*, S. Carnes Harvard. *Secretary*, T. Bert Fletcher, Jr., 1203 Miccosukee Rd., Tallahassee, Fla. Meetings, spring and winter.
- Georgia State Obstetrical and Gynecological Society.** (1951) *President*, Charles Mulherin, Augusta, Ga. *Secretary*, Bothwell Traylor, 455 N. Milledge Ave., Athens, Ga. Meetings, spring and fall.
- Harris, John Warton, Obstetrical Society.** (1953) *President*, William R. Knight, III. *Joint Secretaries*, Madeline Thornton and William Keikhof, State of Wisconsin General Hospital, 1300 University Ave., Madison, Wis. Annual meeting in May.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, Fugate Carty. *Secretary*, John Ohtani, Rm. 410, Professional Center Bldg., Honolulu, Hawaii. Meetings, third Monday of each month.
- Houston Gynecological and Obstetrical Society.** *President*, J. P. Salerno. *Secretary*, William R. Knight, III, 724 Hermann Professional Bldg., Houston 25, Texas. Scientific meetings, January, March, and May. Business meeting, October.
- Indianapolis Obstetrical and Gynecological Society.** (1947) *President*, Sprague H. Gardiner. *Secretary*, John E. Mackey, 3209 N. Meridian St., Indianapolis 8, Ind. Meetings, January, April, and November.
- Interurban Obstetrical and Gynecological Society.** (1949) *President*, Arthur J. Wallingford, Albany N. Y. *Secretary*, E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y. Meeting, October, 1958.
- Iowa Obstetrical and Gynecological Society.** *President*, William C. Keettel, Iowa City, Iowa. *Secretary*, W. B. Goddard, University Hospitals, Iowa City, Iowa. Meetings, May and November.
- Kansas City Gynecological Society.** (1922) *President*, William C. Mixson. *Secretary*, Kenneth E. Nicolay, 4635 Wyandotte, Kansas City 12, Mo. Meetings, September, November, January, March, and May.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, Joseph Liebman, Frankfort, Ky. *Secretary*, Ed. Masters, 107 Fairmeade Rd., Louisville, Ky. Annual meeting in April.
- Long Beach Obstetrical and Gynecological Society.** (1954) *President*, Sydney G. Willner. *Secretary*, Lyle Gray, 8th and Pine Ave., Suite 419, Long Beach 13, Calif. Meetings, first Tuesday of March, June, September, and December.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Walter C. Rogers. *Secretary*, Dan Golenternek, 360 N. Bedford Dr., Beverly Hills, Calif. Meetings, second Tuesday, September, November, January, March, and May.



- Louisville Obstetrical and Gynecological Society.** *President*, Robert C. Long. *Secretary*, Douglas L. Gillim, 501 Heyburn Bldg., Louisville 2, Ky. Meetings, fourth Monday, September, October, November, January, February, March, April and May.
- Madison Obstetrical and Gynecological Society.** (1950) *President and Secretary*, Gerald Kring, 2 W. Gorham St., Madison, Wis. Meetings, first Tuesday each month, September through June.
- Maryland, Obstetrical and Gynecological Society of.** (1929) *President*, Arthur Hoskins. *Secretary*, Harry M. Beck, 700 N. Charles St., Baltimore 1, Md. Meetings, October, December, February, and May.
- Memphis Obstetrical and Gynecological Society.** (1950) *President*, Carey Bringle. *Secretary*, Robert M. Ruch, Suite 302, 899 Madison Ave., Memphis, Tenn. Meetings, second Tuesday, October through May.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, William Howdon. *Secretary*, John M. Schultz, 504 Huntington Bldg., Miami 32, Fla. Meetings, second Thursday, January, March, May, and November.
- Michigan Society of Obstetricians and Gynecologists.** (1924) *President*, Lester E. Bauer. *Secretary*, E. Bruce Foster, 853 Fisher Bldg., Detroit 2, Mich. Meetings, first Tuesday, October, December, February, and April.
- Milwaukee Gynecological Society.** (1951) *President*, Roland S. Cron. *Secretary*, Carlton W. Wirthwein, 425 East Wisconsin Ave., Milwaukee 2, Wis. Meetings, fourth Monday, January, March, May, and November.
- Minneapolis Obstetrical and Gynecological Society.** (1955) *President*, Mancel T. Mitchell. *Secretary*, Francis M. Swain, Medical Arts Bldg., Minneapolis, Minn. Meetings, third Wednesday, September, November, January, and March.
- Minnesota Obstetrical and Gynecological Society.** *President*, Frederick L. Schade. *Secretary*, Edward A. Banner, 200 First Ave., S.W., Rochester, Minn. Next meeting to be announced.
- Mississippi Obstetrical and Gynecological Society.** (1947) *President*, Cecil Knox. *Secretary*, Blanche Lockard, 838 Lakeland Drive, Jackson, Miss. Meetings, May and November.
- Mobile County Obstetrical and Gynecological Society.** (1949) *President*, O. M. Otts, Jr. *Secretary*, A. K. Conditt, 1367 Government St., Mobile, Ala. Meetings, quarterly when called.
- Montgomery County (Ohio) Obstetrical and Gynecological Society.** (1937) *President*, L. O. Fredericks. *Secretary*, A. A. Kunnen, 406 Harries Bldg., Dayton, Ohio. Meetings, third Wednesday of each month.
- Montana Obstetrical and Gynecological Society.** (1946) *President*, Arnold E. Ritt, Missoula, Mont. *Secretary*, Robert H. Leeds, Chinook, Mont. Next meeting, Bozeman, Mont., May, 1958.
- Nashville Obstetrical and Gynecological Society.** (1955) *President*, Joe Anderson. *Secretary*, James Ellis, Nashville, Tenn. Meetings, March, June, September, and December.
- Nassau Obstetrical Society.** (1944) *President*, David G. Warden. *Secretary*, A. F. Rowsom, 21 Weir Lane, Locust Valley, N. Y. Meetings, second Monday, October, December, February, and April.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Roland McSweeney. *Secretary*, William A. Lynch, 1101 Beacon St., Brookline 46, Mass. Meetings, April and October.
- New Haven Obstetrical and Gynecological Society.** (1946) *President*, William Richards. *Secretary*, Virginia M. Stuermer, 42 Trumbull St., New Haven 10, Conn. Meetings, third Tuesday, September, November, January, March, and May.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Felix H. Vann. *Secretary*, Paul Grossbard, 162 Lexington Ave., Passaic, N. J. Meetings, October and April.
- New Mexico Obstetrical and Gynecological Society.** (1947) *President*, Robert P. George. *Secretary*, C. H. Rundles, 211 Oak St., N. E., Albuquerque, N. Mex. Meetings, quarterly, January, March, June, and September.
- New Orleans Gynecological and Obstetrical Society.** (1924) *President*, Abe Mickal. *Secretary*, Julius T. Davis, Jr., 4414 Magnolia St., New Orleans, La. Meetings, October, November, January, March, and May.
- New York Obstetrical Society.** (1863) *President*, Frank R. Smith. *Secretary*, George L. Bowen, 101 East 74th St., New York 21, N. Y. Meetings, second Tuesday, September through May.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, H. Fleming Fuller. *Secretary*, James A. Crowell, 412 N. Church St., Charlotte 2, N. C. Meeting, Mid Pines Club, Southern Pines, N. C., April 25-27, 1958.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Frank Hill. *Secretary*, G. Wilson Hunter, Box 1388, Fargo, N. D. Meetings, May and September.



- Northeastern New York Obstetrical and Gynecological Society.** (1935) *President*, Paul Schultze, Jr. *Secretary*, Thomas F. D'Aurio, 17 State St., Troy, N. Y. Meetings, third Thursday, January, May, and October.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, George T. Allen. *Secretary*, James B. Eskridge, III, 1200 N. Walker, Oklahoma City, Okla. Meetings, February, April, October, and December.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, W. Riley Kovar. *Secretary*, W. H. Taylor, Jr., 3807 Cuming St., Omaha 31, Neb. Meetings, third Wednesday, January, March, May, October, and November.
- Oregon Society of Obstetricians and Gynecologists.** *President*, J. Oppie McCall, Jr. *Secretary*, Otto R. Emig, Rt. 1, Box 281, Lake Grove, Oregon. Meetings, third Friday, October through May, except December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Donald J. Thorp, Seattle, Wash. *Secretary*, Donald W. DeCarle, 2000 Van Ness Ave., San Francisco, Calif.
- Pacific Northwest Obstetrical and Gynecological Association.** (1947) *President*, Paul Rollins, Seattle, Wash. *Secretary*, Clifford L. Fearl, 1133 S.W. Market St., Portland 1, Ore.
- Philadelphia, Obstetrical Society of.** (1868) *President*, Robert M. Hunter. *Secretary*, John P. Emich, Jr., 155 W. Walnut Lane, Philadelphia 44, Pa. Meetings, first Thursday of the month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, John C. Hughes. *Secretary*, Michael A. Guthrie, 128 Carlton House, 550 Grant St., Pittsburgh 19, Pa. Meetings, first Monday, October through May, except January.
- Portland Society of Obstetricians and Gynecologists.** (1928) *President*, Theodore W. Adams. *Secretary*, J. Oppie McCall, Jr., 812 S.W. Washington, Portland 5, Ore. Meetings, fourth Wednesday, September through May.
- Queens Gynecological Society.** (1948) *President*, Joseph Gaetane. *Secretary*, David A. Connors, 166-05 Highland Ave., Jamaica 32, N. Y. Meetings, second Wednesday, October, December, February, and April.
- Rochester Academy of Medicine, Obstetrics and Gynecology Section.** (1939) *President*, Robert Coreoran. *Secretary*, John G. Hamilton, 256 Alexander St., Rochester 7, N. Y. Meetings, as announced.
- St. Louis Gynecological Society.** (1924) *President*, John E. Hobbs. *Secretary*, George Wulff, Jr., 8505 Delmar Blvd., St. Louis 24. Meetings, first Thursday, October, December, February, and April.
- San Antonio Obstetrical and Gynecological Society.** *President*, G. G. Passmore. *Secretary*, Frank M. Posey, Jr., 641 Moore Bldg., San Antonio, Texas. Meetings, first Monday of the month.
- San Diego Gynecological Society.** (1937) *President*, Wilton Lewis. *Secretary*, George Turner, 2330 First Avenue, San Diego 1, Calif. Meetings, as announced.
- San Francisco Gynecological Society.** (1929) *President*, Robert D. Dunn. *Secretary*, Carl Goetsch, 2915 Telegraph Ave., Berkeley 5, Calif. Meetings, second Friday, October through April.
- Seattle Gynecological Society.** (1941) *President*, Paul Peterson. *Secretary*, L. Bruce Donaldson, 532 Stimson Bldg., Seattle 1, Wash. Meetings, third Wednesday, January, March, April, May, September, October, and November.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, William A. Hart. *Secretary*, Albert J. Baroody, Florence, S. C. Meetings, spring and fall.
- South Dakota Society of Obstetrics and Gynecology.** (1952) *President*, Fred Leigh, Huron, S. D. *Secretary*, C. A. Stern, 1320 S. Minnesota Ave., Sioux Falls, S. D. Meetings, May and September.
- Southern California, Obstetrical and Gynecological Assembly of.** (1945) *President*, Daniel G. Morton, Los Angeles, Calif. *Secretary*, Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, Los Angeles, Feb. 10-14, 1958.
- Southwest Obstetrical and Gynecological Society.** (1951) *President*, Charles Van Epps. *Secretary*, Zeph B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz. Next meeting, Phoenix, Ariz., November, 1958.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Arthur M. Faris, Houston, Texas. *Secretary*, Oran V. Prejean, 1317 N. Washington Ave., Dallas 4, Texas. Annual meeting, Galveston, Texas, Feb. 15, 1958.
- Tulsa County Obstetrical and Gynecological Society.** (1955) *Vice President*, Robert E. Dillman. *Secretary*, James T. Maddox, Ranch Acres Medical Center, Tulsa, Okla. Five meetings per year.
- Utah Obstetrical and Gynecological Society.** (1948) *President*, John Z. Brown, Jr. *Secretary*, H. A. Theurer, Jr., 60 S. 4th East, Salt Lake City, Utah. Meetings second Thursday of October, December, February, and May.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Paige E. Thornhill. *Secretary*, Brock D. Jones, Jr., 1204 Colonial Ave., Norfolk, Va. Meetings, April and October.

- Washington Gynecological Society.** (1933) *President*, Stafford W. Hawken. *Secretary*, Robert B. Nelson, Jr., 1824 Massachusetts Ave., N. W., Washington 6, D. C. Meetings, October, December, January, March, and May.
- Washington State Obstetrical Association.** (1936) *President*, Morton W. Tompkins. *Secretary*, Charles W. Day, 1420 Seneca, Seattle 1, Wash. Meetings, spring and fall.
- West Texas Obstetrical and Gynecological Society.** (1954) *President*, Joe L. Cornelison, San Angelo, Texas. *Secretary*, Tom C. Burditt, 1440 N. Third St., Abilene, Texas.
- Westchester Obstetrical and Gynecological Society.** (1939) *President*, Payson B. Ayers, Cos Cob, Conn. *Secretary*, Edwin A. Haverty, 328 Mamaroneck Ave., White Plains, N. Y. Meetings, second Wednesday, October, November, January, February, March, and May.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Ralph E. Campbell, Madison, Wis. *Secretary*, William C. Mussey, 113 N. Carroll Ave., Madison 3, Wis. Spring meeting in conjunction with the Wisconsin State Medical Society.

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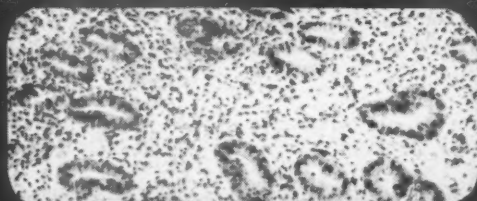
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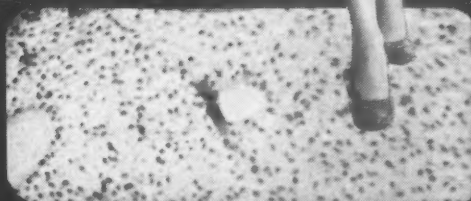
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Pretreatment biopsy from patient with anovulatory menometrorrhagia.  
Interpretation: Proliferative endometrium.



Post-treatment biopsy on day 25 after 10 mg. of Enovid daily from day 5 to day 20.  
Interpretation: Late secretory endometrium with pseudo-decidual stromal development.

Biopsy photomicrographs courtesy of Anna L. Southam, M.D., New York, N.Y.

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Metrorrhagia	One or two 10-mg. tablets daily to day 25 (or for 10 days to establish cycle)	same as above
Amenorrhea (primary or secondary)	One 10-mg. tablet daily for 20 days to establish cycle	same as above
Oligomenorrhea	One 10-mg. tablet daily from day 5 to day 25*	same as above
Premenstrual Tension	One 10-mg. tablet daily from day 5 to day 25*	same as above
Dysmenorrhea	One 10-mg. tablet daily from day 5 to day 25	One 10-mg. tablet daily from day 5 to day 25
Inadequate Luteal Phase	One 10-mg. tablet daily from day 15 to day 25	One 10-mg. tablet daily from day 15 to day 25

\*The administration of Enovid prior to day 15 may interfere with ovulation; if anovulatory cycles are not desired, one 10-mg. tablet of Enovid should be administered daily from day 15 to day 25.

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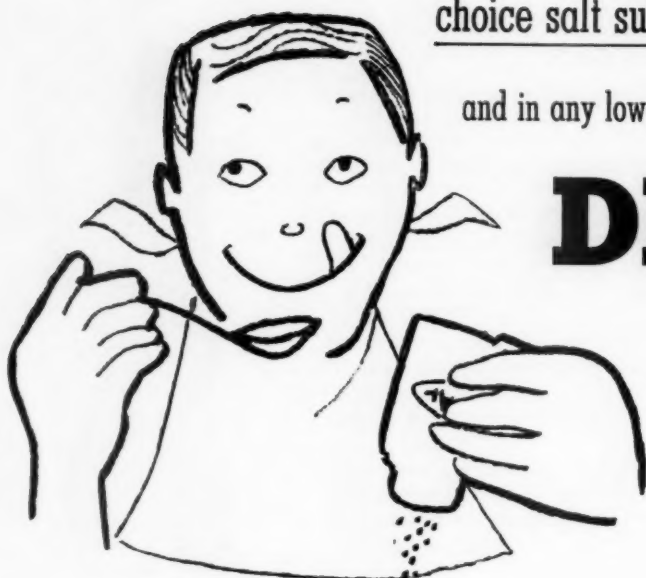
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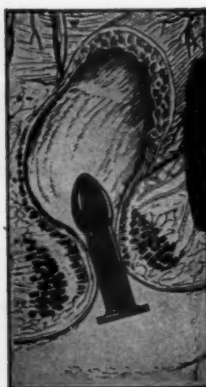
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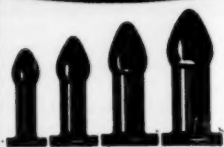
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In the preparation of this revision an attempt has been made to conform to the purpose of the original author—to develop a practical aid to physicians who are meeting and contending with obstetric difficulties and emergencies. Because the general practitioner is often the first to see the complicated cases, the reviser has made a special attempt to make the new edition of as much practical value as possible to the general practitioner without destroying its value for the specialist. To accomplish this he has included methods for the management of pregnancy and its complications which can be utilized in small general hospitals or at home, as well as in large well-staffed maternities.

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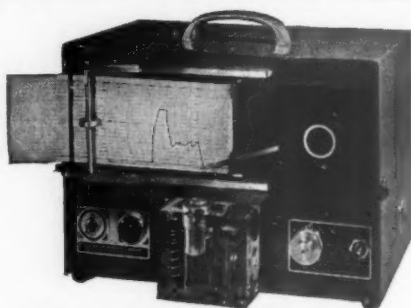
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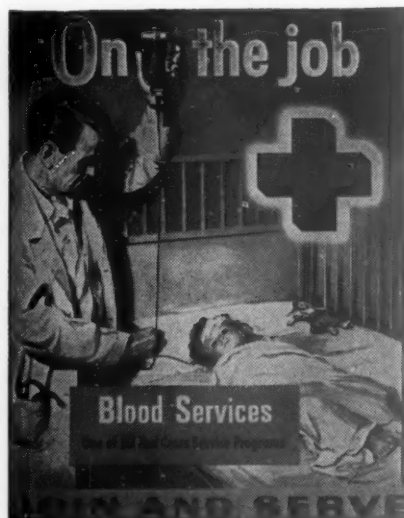
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